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1. Livingston, S., and Petersen, D.: New England J. Med. *254*:327 (Feb. 16) 1956.
2. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.
3. Berman, B. A.: Am. J. Psychiat. *112*:541 (Jan.) 1956.

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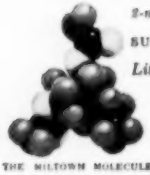

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SECTION ON
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Studies in Headache

Bulbar Conjunctival Ischemia and Muscle Contraction Headache

A. M. OSTFELD, M.D.; D. J. REIS, M.D., and H. G. WOLFF, M.D., New York

Introduction

Studies on bulbar conjunctival vasodilatation and edema occurring during migraine headache have been described and commented upon elsewhere.[1] In the course of these investigations, in order more fully to evaluate the changes seen during a migraine headache attack, the bulbar conjunctival vessels of two healthy, normotensive young male subjects, who seldom, if ever, had headaches, were examined daily for 23 days. The examination was made by means of a Poser ophthalmic slit lamp at a magnification of ×47.5, and appropriate photographs were made. Certain solutions prepared in an isotonic phosphate buffer at a pH of 7.2 and topically applied were employed to assess vascular reactivity. The least concentration of topical levarterenol required to blanch capillaries was determined and was called the sensitivity threshold. In the 46 examinations made on the two healthy subjects no vasodilatation or migraine headache occurred. However, on five occasions there were increased arteriolar constriction and vasomotion (spontaneous rhythmic interruption of blood flow), decrease in number of patent capillaries, and an increased sensitivity to levarterenol. There was no correlation between such bulbar conjunctival ischemia and time of day, food intake, mild to moderate exercise, or prolonged close reading, although on three occasions the blood pressure of the two subjects, while still within normal limits, was slightly elevated over previous levels. There was, however, a predictable change in feeling state and behavior, evident in each of the five instances in which bulbar conjunctival ischemia was observed. These episodes occurred at times during which the subjects were tense and apprehensive and were engaged in matters which they felt required an unusual degree of alertness and effort. The following studies were begun initially to evaluate more fully the relationship between bulbar conjunctival ischemia and the feeling state and behavior described above. Subsequently, possible relevance to muscle contraction headaches was assessed, and experiments were undertaken to determine the mechanism of the bulbar conjunctival ischemia.

Submitted for publication Aug. 20, 1956.

From the Study Program in Human Health and the Ecology of Man, Departments of Medicine and Psychiatry, New York Hospital-Cornell Medical Center.

Present Study

SERIES 1.—*Evaluation of a Possible Relationship of Life Situations, Behavior Patterns, and Bulbar Conjunctival Ischemia.*—To ascertain the relationship, if any, between a single, clearly definable stressful life experience and bulbar conjunctival appearance and behavior, the following study was made. Eight healthy, normotensive male medical students were examined in association with a final examination in physiol-

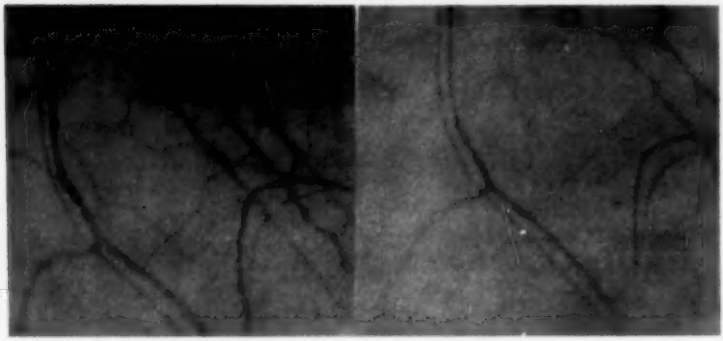

Fig. 1.—Effect of topical levarterenol on bulbar conjunctival vessels. Those at the right are untreated. At left the response to the threshold amount is shown. × 90.

ogy. Specifically, after a 10-minute period of rest, pulse, blood pressure, conjunctival vascular appearance, and levarterenol sensitivity threshold (Fig. 1) were determined six and two days before the examination, on the day of the examination, and two days afterward. A statement concerning mood and feeling state was obtained from each subject, and pertinent notes were made about motor and verbal behavior, bodily attitudes, and general appearance. The mean averages of these observations are shown in Figure 2. In seven of the eight subjects there was a progressive increase in bulbar conjunctival ischemia and levarterenol sensitivity as the examination approached. Predictably, in association with these vascular changes, there were verbal reports of feelings of tension, and, on inspection, some rigidity of body posture, increase in hand and foot movements, jerkiness and rapidity of speech, and impatience with the eye examination. The two subjects exhibiting the greatest degree of bulbar conjunctival ischemia also displayed the greatest disturbance in mood and behavior and, in addition, significant elevation of systolic and diastolic blood pressure. In the same seven subjects there was a decrease in bulbar conjunctival ischemia and levarterenol sensitivity, as well as evident "relief" two days after the final examination. For the group as a whole, although the blood pressure fell slightly during the period of observation, there was no direct association between degree of bulbar conjunctival ischemia and level of blood pressure. In the one subject in whom no bulbar conjunctival changes occurred, there was also no evidence of alteration in mood or behavior.

Comment: Although there was no systematic questioning about the occurrence of headache in the above group, the known association between extracranial artery constriction and muscle contraction headache, coupled with similar alterations of feeling state and behavior during such headache, led us to investigate a possible relationship.

Muscle contraction headache commonly presents itself as a bilateral, steady, nonthrobbing, deep aching pain or pressure sensation, not associated with scotomata, nausea, or vomiting, and not occurring in a familial or hereditary distribution, lasting from

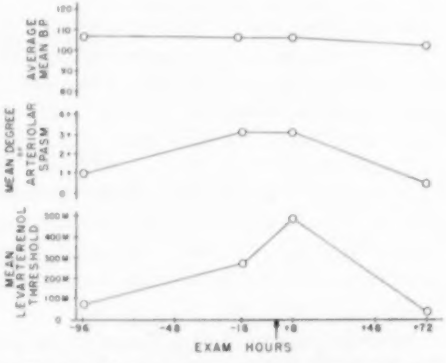

Fig. 2.—Mean averages for levarterenol threshold, degree of arteriolar spasm, and blood pressure for eight normotensive subjects under stress.

minutes to months, not responding to, or being even made worse by, vasoconstrictors. Characteristic locations are the neck and occiput, although the frontal, parietal, and temporal areas are involved. Earlier studies have demonstrated the relevance to muscle contraction headache of increased skeletal muscle contraction and extracranial vasoconstriction,[2] as well as the fact that increased skeletal muscle contraction about the head may occur in life settings evoking anxiety.[3]

SERIES 2.—*Bulbar Conjunctival Vessel Appearance and Reactivity During Frontal Muscle Contraction Headache.*—Eleven persons subject to muscle contraction headache were examined on a total of 30 occasions—before, during, and after such headache experienced frontally. The appearance of the vessels before and after headache differed in no way from the findings in the previously studied group, who had never had headaches.[1] Specifically, there were slight arteriolar vasoconstriction and a moderate number of patent capillaries. The sensitivity to topical levarterenol ranged between 1:50,000 and 1:100,000. During the 14 frontal muscle contraction headaches experienced by the group, there were on 12 occasions bilateral conjunctival ischemia, manifested by increased arteriolar vasomotion and spasm, decreased number of patent capillaries, and an increased sensitivity to topical levarterenol in the range of 1:200,000 to 1:400,000 (Figs. 3 and 4). On one occasion there was largely unilateral bulbar conjunctival ischemia and headache was more intense on the side of the ischemia. When headache persisted for days, the bulbar conjunctival changes persisted also, the two commonly terminating together. Blood pressure in six members of the group was 10 to 25 mm. Hg systolic and 5 to 10 mm. Hg diastolic higher during one or more headaches than readings obtained during tranquil, headache-free periods. The other five exhibited no significant change in blood pressure, i. e., less than a difference of 10 mm. Hg systolic and 5 mm. Hg diastolic in association with headache.

SERIES 3.—*Effects of Vasoconstrictor Agents on Muscle Contraction Headache and on Relevant Large and Minute Extracranial Vessels.*—To assess the relevance of the ischemia to muscle contraction headache, the following experiments were performed: On 12 occasions in five subjects during muscle contraction headache, intravenous levarterenol, an agent with almost purely vasoconstrictor effects, was administered as a 0.008% solution of levarterenol (Levophed) bitartrate in 5% dextrose in water. The agent was administered at a rate sufficient to raise systolic blood pressure 10 to 20 mm. of mercury. On six occasions the subjects were seated and their bulbar conjunctival vessels observed before, during, and after the infusion. On another six occasions the subjects were supine and the temporal artery pulse waves were recorded by means of a capacitance pick-up,

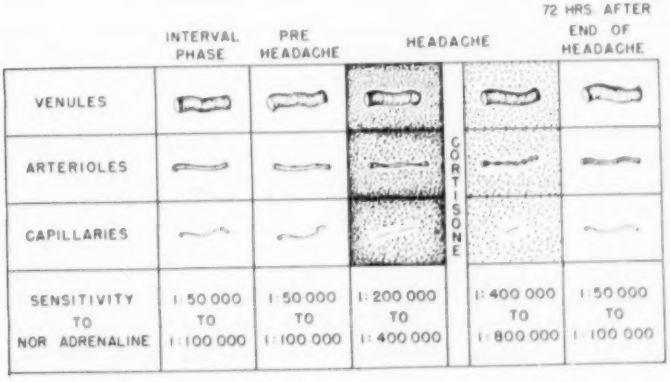

Fig. 3.—Schematic representation of function and sensitivity to topical levarterenol of bulbar conjunctival blood vessels in frontal muscle contraction headache.

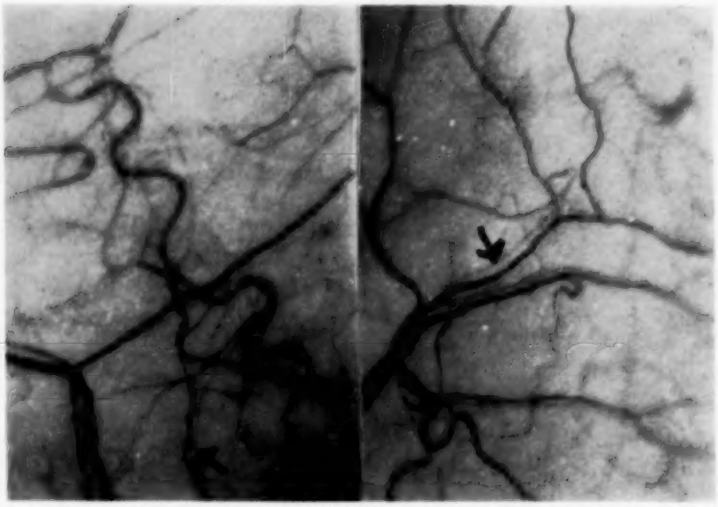

Fig. 4.—Bulbar conjunctival vessels (× 180) during muscle contraction headache. Note the paucity of capillaries and narrowed arterioles (arrows).

transducer, and Sanborn direct-writer electrocardiograph. Whereas administration of levarterenol in amounts sufficient to raise systolic blood pressure 10 to 20 mm. of mercury has never produced headache in subjects without it, on 10 of these 12 occasions there was slight to moderate increase in the severity of the headache. On two occasions the headache intensity remained unchanged. In these observations, examination of the conjunctival vessels and inspection of the amplitude and number of reflected waves in the pulse wave recordings, both indicated vasoconstriction while the agent was being administered and during the time the headache was worsened. With cessation of infusion, the headache intensity decreased, blood pressure returned to previous levels, the bulbar conjunctival vessels exhibited less ischemia, and the pulse-wave amplitudes increased.

Likewise, on five occasions, 0.25 to 0.5 mg. of ergotamine tartrate was administered to five subjects with nuchal and occipital muscle contraction headache. In two subjects there was a moderate increase in headache intensity for two hours; in a third there was a profound increase in severity of the pain, lasting about three hours. In the other two subjects no notable change in pain intensity occurred for periods up to two and one-fourth hours.

Comment: Although muscle blood flow was not determined directly during administration of these vasoconstrictor agents, the vasoconstriction evident in the larger vessels (superficial temporal artery) which terminate in, or smaller vessels (bulbar conjunctival vessels) which parallel, the frontalis muscle blood supply, supports the inference that muscle ischemia also occurred during the period of worsening of headache, whereas, as stated above, a comparable degree of ischemia in the absence of headache does not predictably produce such pain. When increased skeletal muscle contraction, some degree of ischemia, and therefore headache, are present, further vasoconstriction leads to an increase in ischemia and subsequent worsening of the headache.

Series 4.—*Effect of a Vasodilator Agent on Muscle Contraction Headache and Local Ischemia.*—The effects of an increase in local blood flow were assayed in the following series of experiments: On six occasions amyl nitrite by inhalation was administered to five subjects with muscle contraction headache. The pulse-wave changes were recorded in three instances; the bulbar conjunctival vessels were studied in the other

three, and, as well, the blood pressure and the duration and intensity of facial flush. The amount inhaled was limited to prevent a decrease in blood pressure of more than 15 mm. systolic pressure. The anticipated effects of the agent occurred in all cases, namely, facial flush, increase in amplitude of temporal artery pulse waves, slight to moderate bulbar conjunctival vasodilatation, and minimal blood pressure. These changes persisted for from two to five minutes after cessation of inhalation. On five of the six occasions there was a decrease in the intensity of headache; on one occasion, no change. The alleviation of headache, however, persisted only two to three minutes longer than the induced vasodilatation.

Comment: It is inferred that a transient increase in local blood flow affords transient and partial relief of head pain. However, the increased skeletal muscle contraction and mechanisms causally related to the accompanying vasoconstriction were unaffected, and, with disappearance of the induced vasodilatation, headache returned to its previous intensity.

It having been established that bulbar conjunctival ischemia is relevant to muscle contraction headache, studies to determine the mechanism of such ischemia were undertaken. Experiments were designed to assay the importance of neurogenic and certain humoral mechanisms in inducing bulbar conjunctival vasoconstriction.

SERIES 5-6.—*Neurogenic Component in Bulbar Conjunctival Ischemia.*—Effects of a Ganglionic-Blocking Agent (Series 5): The effects of a ganglionic-blocking agent on bulbar conjunctival ischemia during muscle contraction headache were ascertained. Twenty-five milligrams of hexamethonium bromide was dissolved in 500 cc. of 5% dextrose in water and administered intravenously on two occasions to two subjects experiencing such headache bifrontally. The rate of infusion was sufficient to produce a fall in mean blood pressure of 40% or more in each case, with the subjects in a reclining position, and, as well, dry mouth, inability to urinate, and blurring of vision. The bulbar conjunctival ischemia appeared in no way affected during the administration of this agent for periods up to 35 minutes, and headaches were reported unchanged during this time.

Effects of Cervical Sympathectomy (Series 6): A subject, who had a left stellate ganglionectomy on Jan. 20, 1954, and a right cervical sympathectomy on Feb. 9, 1954, and who, as well, experienced intermittent muscle contraction headaches, was examined. In this subject, bilateral ptosis and absence of facial sweating on starch-iodine-heat testing evidenced continuing sympathetic denervation. During tranquil and headache-free periods the bulbar conjunctival vessels appeared "normal," except that there was an increased sensitivity to topical levarterenol of 1:150,000 concentration in the right eye and 1:200,000 concentration in the left eye. On two occasions the examination was performed during frontal muscle contraction headache, occurring in a setting of apprehension and unusual effort. On both occasions there were increased arteriolar vasoconstriction and vasomotion, and the levarterenol sensitivity rose to from 1:600,000 to 1:800,000 in both eyes.

Comment. The persistence of bulbar conjunctival vasoconstriction during frontal muscle contraction headache after ganglionic blockade or surgical sympathectomy supports the thesis that neurogenic influences have little or no relevance to such vasoconstriction. There remain the possibilities that local alterations in intrinsic vascular tone or humoral agents or both are concerned. A series of experiments to assess a possible relevance of certain humoral agents was undertaken.

SERIES 7.—*Humoral Component in Bulbar Conjunctival Ischemia.*—Effects of Cortisone (Series 7): The potentiating effects of cortisone on levarterenol [4] and the bulbar conjunctival ischemia described in Cushing's syndrome,[5] coupled with the fact that 17-hydroxycorticosteroid excretion is increased during stressful life experience [6] led to the assessment of increased cortisone

activity as a possible ischemia-inducing mechanism in the bulbar conjunctival vessels. Oral cortisone in doses of 25 to 125 mg. was given on 13 occasions to three intact young male patients, one of them subject to muscle contraction headache. All doses below 50 mg. had no effect on bulbar conjunctival vessels, whereas doses between 50 and 75 mg. were unpredictable in their effect. Only at 100 mg. or more was there a predictable occurrence of bulbar conjunctival ischemia one to four hours after administration. Headache was not induced on any occasion.

Comment. Since Silber's data[7] indicate that in normal subjects the upper limit of adrenal glucocorticoid production is about 30 mg. in 24 hours, it is unlikely that steroid production could ever attain such levels as alone to induce bulbar conjunctival ischemia. It remains possible that increased steroid production in combination with other factors may influence the appearance of the vasoconstriction.

Effects of Levarterenol (Series 8): The known vasoconstrictor effects of levarterenol and the fact that levarterenol urinary excretion is increased during certain stressful experiences[8] led to an assessment of its possible role in such ischemia. It was administered intravenously to four persons subject to muscle contraction headache during headache-free periods at rates sufficient to produce the same degree of bulbar conjunctival ischemia and topical levarterenol sensitivity that these patients exhibited during headache. Headache was not induced on any of these occasions, and systolic blood pressure at these rates of infusion of levarterenol was elevated by 25 to 40 mm. of mercury.

As described in Series 3, blood pressure elevation in 11 subjects during muscle contraction headache was slight in degree, if present at all. Since the amount of levarterenol required in these same subjects to produce bulbar conjunctival ischemia equal to that present during headache also raised blood pressure more than ever occurred during headache, it is unlikely that levarterenol alone is the determinant of such ischemia.

It is significant, however, that a naturally occurring vasoconstrictor agent, in amounts not far outside physiological ranges, induces a bulbar conjunctival ischemia pattern identical with that seen during muscle contraction headache.

Effects of an Adrenolytic Agent (Series 9): The following experiments were undertaken to assess the effect on muscle contraction headache of reducing the effective concentration of levarterenol and epinephrine by introducing an adrenolytic agent. Ten milligrams of phentolamine hydrochloride was given intravenously on three occasions to three subjects when they were experiencing muscle contraction headache and, as well, bulbar conjunctival ischemia. For from 3 to 10 minutes there was a decrease in headache intensity and moderate fall in blood pressure (20 to 30 mm. of mercury systolic, 10 to 20 mm. of mercury diastolic), and bulbar conjunctival vessels exhibited a slight decrease in vasomotion and increase in the number of patent capillaries. Such effects were all terminated within 10 minutes after administration of this agent, and the headache, blood pressure, and bulbar conjunctival vessels returned to their previous states.

Comment. The fact that an adrenolytic agent transiently reduces headache intensity and bulbar conjunctival ischemia during muscle contraction headache further supports the thesis that the level of circulating catechol amines is relevant to the ischemia.

General Comment

Whereas it is established that decreases in local neurogenic vasomotor influences have no effect on bulbar conjunctival vessel ischemia, alterations in concentration of two humoral agents, cortisone and levarterenol, have significant effects. Because the amounts of oral cortisone required to produce conjunctival vasoconstriction are larger than normal adrenals can produce in the same

period of time, it is unlikely that such steroids have more than a supportive role in inducing ischemia. However, changes in the concentration of circulating levarterenol, which are not far in excess of alterations that might occur in "daily life" in normal humans, have a prominent effect on bulbar conjunctival vessels. It is inferred that increases in circulating catechol amines occurring in life settings evoking feelings of anxiety and tension may initiate or intensify ischemia about the head and are thereby relevant to muscle contraction headache.

Summary and Conclusion

During life situations evoking anxiety and apprehension and behavior patterns of increased alertness and activity, there occurred predictably bulbar conjunctival vasoconstriction and arteriolar hypersensitivity to topical levarterenol.

During frontal muscle contraction headache, bulbar conjunctival ischemia predictably occurred.

Induction of extracranial ischemia in persons subject to muscle contraction headache, during headache-free periods, did not produce headache.

Agents promoting extracranial ischemia intensified muscle contraction headache; vasodilator agents alleviated muscle contraction headache.

Ganglionic blockade and surgical sympathectomy had no significant effect on the bulbar conjunctival ischemia present during muscle contraction headache.

When the effective amount of circulating catechol amines present during muscle contraction headache was altered either by infusion of levarterenol or by administration of an adrenolytic agent, there was a parallel between the intensity of bulbar conjunctival vessel ischemia and levels of circulating catechol amines, a finding which supports the thesis that these agents are relevant to such vasoconstriction.

Increased skeletal muscle contraction about the head and humorally influenced extracranial vasoconstriction are parallel responses to certain life situations and acting together, in some persons, induce muscle contraction headache.

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Face-Hand Test Responses of Psychotic and Mentally Defective Patients

The Relation of Age to Sensory Errors in Chronic Patients

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Introduction

The remarkable observation that many persons do not perceive one of two simultaneous tactile stimuli though each one is recognized when applied separately has been carefully studied independently by Bender and associates [1] and Cohn.[2] When the cheek and dorsum of the hand are used as sites for simultaneous stimulation, the procedure has been referred to as the face-hand test.[3] By this method it has been shown that normal children between 3 and 6 years of age [4] and normal adults over 65 [5] fail to discern the hand stimulus more frequently than do other age groups. It has also been shown that adult patients with organic mental syndrome [3] and mental defectives [6] make more perceptual errors with the face-hand test than normal adults of the same age. Such lack of percept of one of the two simultaneously applied stimuli has been termed "extinction" by Bender.[7] Aphasic and schizophrenic patients [1] are reported to give results similar to normal adults in this regard.

Fink and associates [3] consider persistent errors made by this method as a diagnostic sign of organic mental syndrome. Cohn [2] has hypothesized that when clinical extinction is observed, the basic condition for the dissolution of perceptual organization in adults is the presence of structural changes in the central nervous system, primarily of the thalamoparietal projection system. The site of such damage also has been ascribed by Critchley [8] to certain parts of the cerebral cortex, namely, the parietal lobe or its thalamic connections, and such damage is considered by Cohn [9] to result in a regressive simplification of the body-image concept into the childhood pattern.

The basic patterns of response to the face-hand test have been established, and the factors affecting the results are well known.[10,11] Since it has been shown that normal subjects fail this test more frequently as the age of the group tested increases, this investigation was designed to ascertain whether chronic mental patients and mentally defective patients display a greater number of test failures with advancing age than do normals. This report is concerned with the findings on 368 subjects which indicate that mentally defective and chronic psychotic patients manifest a greater number of failures on the face-hand test with aging than is the case with normal persons.

Subjects

The subjects studied were of three main groups: a normal control group, mental patients with psychosis, and mentally defective patients of both sexes. One hundred seventeen normal subjects were obtained as controls by testing employees of the Galesburg State Research Hospital. These were subdivided for analysis into a group under 40 and one from 40 to 64 years of age. The age range, average age, and total number in each of these groups are presented in the accompanying Table.

The chronic mental patients with psychosis were divided upon clinical diagnosis into a schizophrenic and a nonschizophrenic group. No attempt was made to study separately the clinical types of schizophrenia or to subdivide the nonschizophrenic group into the various types incident to this group, such as manic-depressive psychosis and involu-

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From the Thudichum Psychiatric Research Laboratory, Galesburg State Research Hospital.

Face-Hand Test Population and Response Data

Subject Class and Age Range, Yr.	Mean Age ±S.E.M., Yr.	No. of Subjects	Initial No. of Errors on Hand Percept	No. of Test Failures	Per Cent Failure
Normal					
17-39	25.21±0.76	63	31	0	00.00
40-64	52.85±1.25	54	29	3	5.56
Mentally defective patients					
16-30	23.82±0.20	56	49	24	42.86
45-56	49.65±0.40	57	52	37	64.91
Schizophrenic patients					
40-64	54.41±0.98	46	39	20	43.47
65-74	69.28±0.53	30	25	16	53.33
Nonschizophrenic patients					
40-64	56.84±1.28	25	20	11	44.00
65-74	68.23±0.48	37	32	17	45.94

tional melancholia. All of these patients were tested on the wards of the Galesburg State Research Hospital and were selected by the attendants for their cooperativeness. Their histories were studied after the examination. Only persons over 40 were studied statistically because the patient population readily available was almost exclusively in this category. The psychoses of these patients were designated as chronic because the average duration of hospitalization for mental disease of these subjects was approximately 18 years. No patient with an early diagnosis of organic syndrome was used for statistical analysis because it was felt that these patients would not have changed throughout the years, since such patients are known to fail the face-hand test consistently.[8] The total number, age range, and average age for these patients are shown in the Table.

The mentally defective subjects studied were obtained from the wards at the Galesburg State Research Hospital and from the Lincoln State School and the Dixon State School. These patients were selected at random by the men in charge; the only request was that they were to be selected on the basis of two age groups: one under 30 and one over 45 years of age. The Table shows the number, age range, and mean age of these two groups of patients. None of these subjects was found to show any gross mental symptoms or cerebral disease, such as disorientation, hemiplegia, or Parkinsonism. Furthermore, since the results of the face-hand test have been shown to vary with the mental age of the mentally defective subject,[6] it is important to mention that the mental age distribution for both these groups was comparable and within a 3-year-6-month to 11-year range.

Method

The subject to be tested was seated in a chair with his arms on the arms of the chair. During the examination each subject was instructed to close his eyes while the dorsum of the hand and the cheek of the face were simultaneously touched or stroked ipsilaterally with a cotton pad. The subject was then asked what was felt and also to localize the stimuli. This procedure was then repeated on the contralateral side. If only one percept was recognized, the subject was asked whether any other stimulus was felt. When only one stimulus was perceived, it was almost always the facial one, indicating a dominance of the face over the hand, and was referred to as a face-dominant response.[6] This method of examination was continued until at least 10 successive trials of simultaneous tactile stimuli were applied or until the subject correctly perceived both stimulations in less than 10 trials. The subject was considered to have failed the face-hand test if only the face stimulus was felt after 10 consecutive trials.

If the subject perceived only the face stimulus after 10 consecutive trials of double simultaneous tactile stimulation, he was shown the method of examination and the test was then again repeated on the same person several times to determine whether this knowledge of the test would change the results. Furthermore, the hand was separately stimulated during the examination period in those subjects who persistently felt only the face stimulus when the face-hand test was applied in order to establish whether the subject was capable of this perception. The few patients who displayed an allesthesia,[12] exosomesthesia, or displacement[13] by this method of examination are not included in this report.

Results

Figure 1 shows clearly that a greater number of mentally defective patients made 10 or more consecutive errors on the face-hand test than did normals of comparable age. Thus, none of the 17-39- and only 5.6%

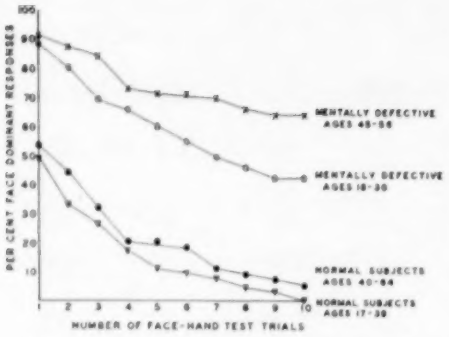

Fig. 1.—Responses to successive face-hand test trials of normal control subjects and mentally defective patients of two different chronological age groups. It is apparent that the mentally retarded subjects displayed more sensory errors than the normal persons and that the older group of mentally defective patients made significantly more errors than the younger group.

of the 40-64-year age group of normal subjects failed, whereas 42.9% and 64.9% of the 16-30- and 45-56-year age group of mental defectives, respectively, did not perceive the hand stimulus in 10 or more trials with this test. Furthermore, it is apparent that the number of older mentally retarded patients missed more frequently than did the younger group. A χ^2 analysis also indicates this difference and yields a probability value of $<0.02>0.01$. The slight difference between the older and younger normal groups is not significant. The number of initial test errors and test failures of the total examined for each of these groups, as well as the percent failure, is summarized in the Table.

Approximately 44% of all the chronic psychotic patients between the ages of 40 and 64 manifested a face dominance at the end of 10 face-hand trials. In contrast, only 5.6% of the normal control subjects for this age group showed a similar error (Fig. 2). It is also apparent from Figure 2 that the number of test failures for chronic psychotic patients between 65 and 74 (49.3%) is not appreciably greater than that observed in the 40-64-year age range (43.7%). The results obtained with the schizophrenic and nonschizophrenic patients in the 40-64-year age group closely paralleled each other (Table), and consequently the curves representing these two groups in Figure 2 reflect the percent face dominance observed with each group separately. As shown in the Table, the test results of the schizophrenic and nonschizophrenic patients between the ages of 65 and 74 were not so closely related, but, nevertheless, were combined in Figure 2 in order to observe the possible effect of age on this test by patients with a long history of hospitalization.

Similarly, an analysis of the initial trials reveals that fewer normal and younger subjects made errors on the face-hand test than was the case with the patients (Table). Thus, the hand stimulus was not recognized in approximately 50% of all the normal subjects on the first test trial, whereas 87% of the younger and 91% of the older mentally defective subjects failed to perceive the first stimulus. Likewise, 83% of the 40-64-year age group and 85% of the 65-74-year age group of psychotic patients did not respond to the hand stimulus on the initial trial.

Comment

Since persistent errors on the face-hand test are considered a diagnostic sign of organic brain syndrome[3] and parietal lobe damage,[8] the findings on the mentally re-

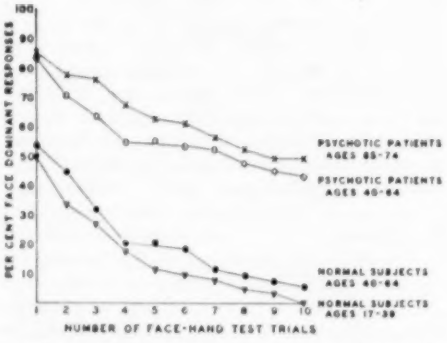

Fig. 2.—Responses on successive face-hand test trials of normal, control subjects and chronic psychotic patients. A comparison of the normal group of between 40 and 64 years of age and the chronic psychotic patients of the same age range reveals a significantly greater number of sensory errors committed by the latter group.

tarded patients reported in this paper may be interpreted to indicate that brain deterioration in these patients is more evident at an earlier age than with normal subjects of comparable age. Moreover, such deterioration is more accelerated with an advance in age. Fink and associates [6] reported that 50% of the mentally defective adults examined within the chronological age range of 13 to 41 revealed a face-dominant response with 10 or more trials on the face-hand test, a value approximately midway between the young and the older mentally retarded group in our study. A similar percent face dominance of 53.9 is derived by combining and analyzing these latter two groups (Table). Thus, the upper age range and percent face dominance obtained from the previous report on such subjects are comparable to the mean values obtained from both mentally defective groups reported in this paper. This comparison suggests that brain deterioration is a progressive phenomenon in this type of patient, at least within the chronological age range of 13 to 56.

If brain deterioration is progressive with age, as it appears to be with mentally defective and normal adults above 65,[5] it is difficult to explain why the 65-74-year age group of psychotic patients tested did not reveal a much higher incidence of error than the 40-64-year age population (Fig. 2). Perhaps an early perceptional discrepancy is peculiar to many psychotic patients who may manifest organic changes early in the course of illness, whereas the others follow a course more typical of normal persons. On the other hand, these results may indicate that many chronic psychotic patients mimic an organic brain syndrome which is not apparent in normal subjects. In this regard, Rorschach findings show a more rapid deterioration (constriction) among many institutionalized subjects with an increase in age than is observed in normals, but at upper age limits the results obtained by this test appear similar.[14]

Similarly, the results obtained with the chronic psychotic patients would indicate a more rapid brain deterioration than is seen in normals. The number of errors recorded for the schizophrenic group in this report is considerably higher than that found by Bender and associates.[1] It seems unlikely that this difference is due to experimental error, since our results obtained from the normal control group do not differ significantly from theirs. This discrepancy may be due to the fact that the number of perceptual errors made on the face-hand test is known to increase with age.[5] Since Bender and colleagues do not disclose the age range of the schizophrenic population in their study, an age comparison of his sample and the schizophrenic group of this report is not possible. However, the factor of age in normals does not become particularly important unless the subject is over 65,[5] and it is interesting to note that none of the eight schizophrenic patients tested who happened to be under 40 (age range 26-37) failed the face-hand test. Consequently, the possibility exists that these patients show more marked brain changes earlier than do normal subjects. Presumably, the same reasoning would apply to the other psychotic groups tested, since the results were comparable to those obtained with the schizophrenic subjects. The influence of mental age on this test may be discarded, inasmuch as the recorded mental ages of the psychotic patients were within normal limits.

The possibility that these results are attributable to inattention instead of perceptional difference of organic origin between the patients and the normal control subjects should be considered. Such an hypothesis seems unlikely, for the following reasons: First, a loss of the hand percent only would have to be postulated; second, the errors made on the face or hand stimuli should be distributed approximately one-half by chance (Bender and associates [1]); third, a contralateral deficit for the hand stimulus alone is observed in patients with unilateral lesions of the parietal lobe (Critchley [8]), and therefore inattention would occur only on one side of the body, and, finally, extinction occurs in children [4,15] and a similar phenomenon is observable in fetuses.[16] Furthermore,

many of the patients were retested at a later date with identical results, a procedure which minimizes the chance that the first test results was due only to inattentiveness.

There is also the possibility that a conceptual rather than a perceptual difference exists between patients and the normal subjects. This possibility is inferred by the poor test results obtained from most mentally retarded subjects and the psychotic patients, who generally are disorientated. These same subjects may then do more poorly on the face-hand test as they become older because of the "vegetative" existence incident to prolonged hospitalization. If this is the case, it is difficult to explain why those patients who consistently failed the face-hand test perceived correctly homologous double simultaneous stimuli. Even when those that failed the test (including the three normal subjects) were explained the test procedure and seemingly understood the method, they failed on subsequent examinations. Furthermore, many of the reasons presented above against inattentiveness as a possible cause of test failure may be applied to this situation. Parenthetically, it may be mentioned that many of the patients who failed this test responded favorably to perimetry examinations, indicating that they were capable of responding to two or more simultaneous stimuli (considering the background as a third stimulus) when not tactile.

Fink and associates [3] concluded from their studies that the face-hand test may have diagnostic value in differentiating the patient with an organic mental syndrome from the adult normal and schizophrenic subjects. These authors tested a series of patients with unknown histories at the time of admission to the Bellevue Psychiatric Hospital and found that those patients who showed errors on repeated trials with the face-hand test were subsequently disclosed to have an organic mental syndrome by psychiatric examinations. That the face-hand test may reveal organic brain changes is also supported by other studies on the effects of drugs, brain surgery, hemiplegia, and electroshock therapy.[7,11] If this is true, then our patients, all of whom had long histories of hospitalization and mental illness, may have been suffering from heretofore unrevealed brain damage in addition to a psychosis. It may be that an organic brain change is frequently associated with such protracted mental illness.

Even though there appears to be a correlation between the age of the institutionalized patients and the number of sensory errors they commit, there is no adequate explanation as to why these subjects manifest earlier brain changes than control, noninstitutionalized subjects. The evidence cited from the literature indicates that such test failures are associated with brain changes of an organic nature, which may or may not be irreversible. A series of biochemical, neuroanatomical, and psychophysiological studies are being conducted at the Galesburg State Research Hospital which should add further to our understanding of the aging process and possibly form a rational basis for explaining the findings disclosed in this report.

Summary

A series of face-hand tests (double simultaneous tactile stimulation) on mentally defective, chronic psychotic, and control normal subjects show that mentally retarded and psychotic patients reveal sensory errors earlier in life than do normal persons. In addition, such patients manifest an increase in the number of sensory errors with an advance in age at a more rapid rate than is discernible in normal subjects. Thus, 0 and 6% of the 17-39- and 40-60-year age groups, respectively, of the normal, control subjects persisted in their errors after 10 test trials. In contrast, 43% and 65% of the mentally retarded group of comparable age range (16 to 30 and 45 to 56 years) showed a persistent incident of error with 10 test trials or more. Similarly, 44% of the chronic psychotic patients between 40 and 64 years of age failed this test. An increase in age span to from 65 to 74 did not appreciably increase the incidence of errors in this type of patient. The possibility

that these results are due to organic brain changes at an earlier age in mentally defective and psychotic subjects than in normal persons is suggested.

Drs. W. W. Fox and J. Albaum, of the Lincoln State School, Lincoln, Ill., and Mr. R. E. Wallace and Dr. H. T. Azeris, of the Dixon State School, Dixon, Ill., assisted in this study.

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Mental Function and Cerebral Oxygen Consumption in Organic Dementia

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The aim of the present investigation has been to contribute to the clarification of the clinical diagnosis of slight organic dementia. The commonest group of such patients comprises middle-aged and elderly persons for whom symptoms and anamnestic information suggest some mental reduction. Such patients are usually described as "cases of beginning presenile/senile cerebral arteriosclerosis." However, this diagnosis is often not well founded, as the presence of dementia is frequently difficult to assess; whether the possible dementia is of organic or functional origin is uncertain, and the arteriosclerotic origin of the possible cortical lesion is likewise uncertain.

This report is concerned with the relationship between the cerebral metabolic rate of oxygen ($CMRO_2$) and certain mental functions; the middle-aged patients studied ranged from persons with normal mental function to patients with unquestionable dementia.

Clinical Data

The material consisted of 19 hospitalized patients. Clinically they fell into three groups.

Group 1.—Normal Mentation: This group consisted of six subjects, aged 26 to 67, suffering from various diseases not affecting the brain. All were alert and were on independent clinical evaluation considered mentally normal. The blood pressures of these patients were below 140/100 mm. Hg, and the ocular fundi were normal except in the oldest patient (Case 6), who showed moderate variations in the diameter of the retinal arteries.

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Group 2.—Questionable Dementia: On independent examination the three patients comprising this group gave the impression of some degree of defective mentation, but a definite diagnosis of dementia could not be made clinically. Two of these patients (Cases 7 and 8) were able to carry out their jobs as housewife and barber, respectively. The third patient (Case 9), a former first mate, was invalided by reason of pronounced Parkinsonism. The blood pressures were below 140/100 mm. Hg in these three patients, and in all of them the retinal arteries showed abnormal variations of caliber. Air encephalography showed questionable cortical atrophy of the frontal lobes and normal ventricular system in Case 7 and ventricular enlargement (no air on the convexity) in Case 9. Case 7 had had psychomotor seizures two to three times a day during the past year. Electroencephalography showed marked abnormalities, with a normal dominant frequency but many 6-to-7-per-second and some 3-per-second waves, as well as sharp waves of high amplitude, mostly in the right temporal region. The tracing in Case 9 was normal.

Group 3.—Dementia: This group comprised 10 patients. Dementia was diagnosed independently on clinical evidence of reduced mental capacity, mainly based on the history of previous and present occupation, on interviews with the relatives of the patient when necessary, and on the general behavior of the patient. All 10 patients could be presumed to have been mentally normal prior to the current disease. The degree of dementia was loosely designated as "moderate" (+, Table) or "marked" (++, Table) according to whether it was only just noticeable or very obvious. Most of these patients were unable to manage their previous jobs by reason of their mental disability, only two (Cases 15 and 16) being still at work, on very simple routine tasks. All but one (Case 14) could manage personal requirements. Most showed minor emotional abnormalities, such as emotional incontinence or apathy. No patient was confined to bed, and no patient was under institutional care. None had complicating non-neurological diseases. The mean age was 55 (range 42 to 64) years.

Air encephalography was performed in five cases, and cortical atrophy was found in all five, being associated with ventricular enlargement in three

cases. Electroencephalography was carried out on six patients, and abnormal tracings were obtained in all of them (details given in the case histories below).

The group was homogeneous insofar as all the 10 patients suffered from chronic degenerative cerebral diseases. With regard to the etiology of the cerebral disease, however, the group was not homogeneous: Vascular etiology was suspected clinically in six cases. Two cases were diagnosed as cryptogenic cerebral atrophy. Syphilis and cerebral disease following acute anoxia covered one case each.

Case Histories of Ten Patients with Dementia

CASE 10.—Man, 42. Diagnosis: cerebral arteriosclerosis. Seven years before admission sudden left-sided hemiplegia. Now moderate dementia and slight spastic paresis of left arm. Normal ocular fundi; blood pressure 130/100 mm. Hg. Air encephalography (AEG): cortical atrophy and ventricular enlargement.

CASE 11.—Man, 52. Diagnosis: cerebral anoxia. Cardiac asystole for approximately 10 minutes during anesthesia; cardiac massage; patient unconscious for three days; gradual improvement. When examined two months later, he was moderately demented but otherwise normal. Reflexes and ophthalmoscopy normal; B. P. 125/80 mm. Hg. AEG: cortical atrophy and ventricular enlargement; electroencephalography (EEG): diffuse low frequency (4-6 waves per second).

CASE 12.—Man, 49. Diagnosis: cryptogenic cerebral atrophy. For two years epileptic seizures and gradual mental reduction. Now moderate dementia. Reflexes and ophthalmoscopy normal; B. P. 150/90 mm. Hg. AEG: cortical atrophy and normal ventricular system; EEG: borderline, with a normal dominant frequency and a little 7-per-second and occasional 4-per-second activity.

CASE 13.—Man, 58. Diagnosis: cerebral arteriosclerosis. Gradual mental deterioration for two years. Now marked dementia. Reflexes normal; abnormal variations in diameter of retinal arteries; B. P. 140/90 mm. Hg. EEG: focal abnormalities, consisting of runs of sharp waves and spikes in the left hemisphere, especially temporal.

CASE 14.—Man, 58. Diagnosis: cerebral syphilis. Progressive mental reduction for about five years. Now marked dementia. Abnormal variations in diameter of retinal arteries; B. P. 170/100 mm. Hg. AEG: pronounced cortical atrophy and ventricular enlargement.

CASE 15.—Man, 61. Diagnosis: cerebral arteriosclerosis. Restlessness of calf musculature and moderate dementia, of unknown duration. He was able to manage his work as shoemaker. Reflexes normal; abnormal variations in diameter of retinal arteries; B. P. 105/60 mm. Hg; no definite signs of arteriosclerosis of the lower extremities.

CASE 16.—Woman, 51. Diagnosis: cerebral arteriosclerotic-hypertensive disease. For two years epileptic seizures. In spite of moderate mental reduction, she was able to manage her work as a housewife, aided by a maid. Minor reflex differences; abnormal variations in diameter of retinal arteries and Gunn's sign; B. P. 170/110 mm. Hg. AEG: pronounced cortical atrophy, normal ventricular system; EEG: grossly abnormal, with a normal dominant frequency and many runs of 3-to 4- and 6-to 7-per-second waves, most prominent in the right temporal region. Paroxysmal abnormalities under photic stimulation.

CASE 17.—Man, 59. Diagnosis: cryptogenic cerebral and optic nerve atrophy. Very marked mental reduction for two years and reduced visual acuity (optic nerve atrophy). Reflexes and retinal arteries were normal.

CASE 18.—Man, 64. Diagnosis: cerebral and spinal arteriosclerotic-hypertensive disease. Gradual mental reduction for about one year. Now marked dementia. Bulbar speech and muscular atrophy of spinal type in both arms. A minor retinal hemorrhage and abnormal variations in the caliber of the retinal arteries; B. P. 200/100 mm. Hg. EEG: borderline, with normal dominant frequency and occasional runs of 5- to 6-per-second activity.

CASE 19.—Man, 59. Diagnosis: cerebral arteriosclerosis. Twelve years ago sudden right-sided hemiplegia. For some months rapid and very marked mental reduction. Abnormal variations in diameter of retinal arteries, B. P. 110/80 mm. Hg; four psychomotor seizures in the past three months. EEG: moderately abnormal, with a normal dominant frequency and moderate 5- to 7-per-second activity.

Cerebral Metabolic Rate of Oxygen ($CMRO_2$)

The $CMRO_2$, expressed in cubic centimeters of oxygen consumed per 100 gm. of brain per minute, was determined by the Kr^{85} method,[1] using bilateral internal jugular blood as representative of cerebral venous blood.

The present 19 cases were included in a detailed report of bilateral studies in 38 cases.[2] Each $CMRO_2$ was calculated from 30 inert-gas analyses and 6 oxygen analyses. The standard deviation of the inert gas (Kr^{85}) analyses was 1.6% of the concentrated samples or better, and the standard

deviation of the volumetric [3] or photometric [4] oxygen analyses was 0.16 vol. per cent.

Psychological Method

The psychological diagnosis of the presence and degree of cerebral hypofunction was based on fluctuations in digit learning and deficiencies in abstract behavior as shown by a block-pattern test. (The results of the other psychological tests applied were not used for this purpose.)

Fluctuations in Digit Learning.—Pathological fluctuations were considered to be present if the number of repetitions required to learn two sets of digits of the same length was in the ratio 1:2 or above (+, Table). The only exceptions to this definition were cases in which the difference between the performances amounted to only three repetitions or less, as normal persons may manifest similar minor irregularities under optimal conditions.

The procedure for ascertaining these fluctuations was as follows:

The patient's forward digit span was first determined, the criterion being two of three sets correct. The patient tried to learn a number two digits longer than the span, the psychologist reading the number aloud repeatedly at the rate of one digit per second. The patient attempted to say the number after each reading. To be considered learned, the digits had to be repeated correctly three times in succession with interspersed readings. If up to 10 repetitions were sufficient, the experiment was repeated immediately afterward with a new number of the same length. If 10 repetitions were not sufficient, the test was terminated, and the procedure repeated with a number only one digit longer than the forward span. On occasion, the patient could not succeed even on this test, and in such cases numbers equal to the span were attempted.

The number of repetitions required to learn a set of digits was taken to be the number of trials up to and including the first of the three consecutive correct responses. Where numbers equal to the span had to be used, the results were compared with the digit span. The digit-learning test was always repeated on two consecutive days.

Deficient Abstract Behavior.—The patterns from Wechsler's [5] revision of Kohs' [6] block-pattern test were employed. However, no patterns were demonstrated, all nine patterns being used as test figures following oral instructions. The test was otherwise administered, and the performances interpreted, according to Goldstein and Scheerer's [7] procedure, the basic criterion of abnormality (++, Table) thus being that the patient was unable to build one or more of the patterns on Stage I, even after correct solutions on a higher stage.

Patients needing aid in the form of a higher stage on one or more patterns, even though thereafter able to build the pattern(s) correctly on the original Stage I, were also considered to manifest deficient abstract behavior. These patients were marked + in the Table and were regarded as less severely affected than those failing to benefit from aid.

Standard Conditions.—The tests were carried out in a room free from distracting noises and equipment, between 12.30 and 3 p. m., the longest single session lasting one hour, including rest periods between tests. Prior to the introduction of the crucial tests, the patient was given dummy tests to allay possible nervousness, and as a form of preparation, the first session being fully occupied by noncrucial tests. Great care was taken to ensure satisfactory cooperation by the patients, who were fully informed of the nature of the tests they were to be given. They were requested to tell the psychologist as soon as they felt at all fatigued or began to be uninterested in the tests. They were never pressed to continue work if they did not feel so inclined. The patients appeared interested and at ease in the testing situation.

All patients had a minimum of seven years' elementary education, but none had received advanced schooling. None showed signs of neurosis, functional psychosis, or overt gross emotional abnormalities. All had slept well the preceding night. No patient had been subjected to any mental strain on the morning of the session, and in no case had medication been given that could affect mentation. The patient's subjective state was inquired into. Patients with distracting symptoms were excluded.

Two of the first patients studied were excluded from the series (26 and 28), evaluation of the psychological results being considered impossible, due to extraordi-

narily poor education (28), and lack of cooperation (26).*

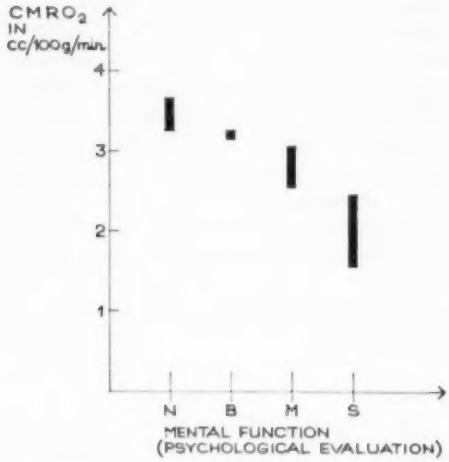
Diagnostic Groups.—The patients were classified psychologically without prior knowledge of the $CMRO_2$. The following four groups were obtained:

Normal: Patients who did not manifest any of the above-mentioned three symptoms

Borderline: Patients who showed only fluctuations in learning

Mild Cerebral Hypofunction: Patients manifesting the milder block-pattern sign, with or without fluctuations in learning

Severe Cerebral Hypofunction: Patients manifesting the severer block-pattern sign



Column diagram of the correlation of cerebral oxygen consumption ($CMRO_2$) and mental function evaluated psychologically, as described in "Correlation of Psychological Data and $CMRO_2$."

N indicates normal subjects (five cases); *B*, borderline group (two cases); *M*, mild cerebral hypofunction (six cases); *S*, severe cerebral hypofunction (six cases).

* The 26th and 28th patients counted from above in Table.*

Results

The results of the clinical, neurophysiological ($CMRO_2$), and psychological studies are presented in the Table, where the patients are listed according to the $CMRO_2$ values.

Correlation of Clinical Data to $CMRO_2$.—It will be remembered that clinically three groups were recognized. The 6 clinically normal patients had a $CMRO_2$ of 3.6 to 3.2 (the unit of the $CMRO_2$—cc/100 gm/min.—will be omitted in the following for the sake of brevity); the 3 questionably demented patients had a $CMRO_2$ of 3.2 to 3.0, and the 10 patients with indisputable organic dementia had a $CMRO_2$ of 2.8 to 1.6. Thus, there was a correlation between the $CMRO_2$ and the degree of the clinically

*Clinical Data, $CMRO_2$ Values, and Psychological Data**

Patient No.	Sex	Age, Yr.	Clinical Evaluation of Dementia†	Cerebral Oxygen Consumption ($CMRO_2$), Cc. O₂/100Gm/Min.	Block-Pattern Test‡	Fluctuations in Digit Learning§
1	M	26	−	3.6	−	−
2	M	55	−	3.6	−	−
3	M	40	−	3.5	−	−
4	M	50	−	3.4	−	−
5	M	61	−	3.3	−	−
6	M	67	−	3.2	−	+
7	F	58	?	3.2	−	+
8	M	55	?	3.0	+	−
9	M	61	?	3.0	+	+
10	M	42	+	2.8	+	+
11	M	52	+	2.8	+	
12	M	49	+	2.6	+	+
13	M	58	++	2.6	+/++	−
14	M	58	++	2.4	++	−
15	M	61	+	2.3	++	−
16	F	51	+	2.1	++	−
17	M	59	++	1.9	++	−
18	M	64	++	1.9	++	−
19	M	59	++	1.6	++	−

* The patients have been listed according to $CMRO_2$ values.

† Degree of organic dementia clinically evaluated as described in text: −, no dementia; ?, questionable dementia; +, moderate, and ++, marked dementia.

‡ Block-pattern test: −, solution on Stage I; +, solution on Stage I after higher stage; ++, failure on Stage I after higher stage. Case 13 managed + the first day but ++ the second day

§ Fluctuations in digit learning −, no fluctuations; +, fluctuations during digit learning. Patient 8 manifested obvious fluctuations during a word-pair learning test.

assessed dementia. However, Cases 15 and 16 had been judged clinically to have only moderate dementia, whereas the $CMRO_2$ was reduced to a level associated with severer dementia in the other cases and the psychological tests showed severe impairment in both. On this basis, it seems that the clinical conclusion that there was only a moderate degree of dementia was erroneous. They were the only patients in the demented group who were able to manage their work, a fact presumably affecting the clinical evaluation of their mentation unduly.

Correlation of Psychological Data and $CMRO_2$ (Fig.).—The psychological tests gave a fourfold division of the material. Psychologically normal patients had a $CMRO_2$ of 3.3 or more. The two patients, 6 and 7, in the borderline group, had $CMRO_2$ of 3.2. Patient 6, aged 67, was the oldest person in the clinically normal group, whereas Case 7 belonged to the clinical group with questionable dementia. Patients with psychologically assessed mild cerebral hypofunction had $CMRO_2$ of 3.0 to 2.6. (One patient with $CMRO_2$ of 2.6, [Case 13] showed the less severe block-pattern sign on the first trial; when tested again, the next day, he manifested the severer sign. In the Table, both + and + + have been entered in the appropriate column, for this reason.) All the patients in this group, with the exception of Case 11 (on whom the digit-learning test was not tried) and Case 8, manifested fluctuations in digit-learning. Patients with signs of severe cerebral hypofunction had a $CMRO_2$ of 2.4 or less. There were no fluctuations in learning.

Additional Observations.—In contrast to bilateral $CMRO_2$, the unilateral $CMRO_2$ of these 19 patients [2] could not be correlated individually with mental function, and we have therefore only given bilateral $CMRO_2$ values in the Table. Various other parameters were determined, but they have not been included in this report, as we do not consider that they give additional evidence of cerebral disease, as will be briefly argued below.

The average bilaterally determined cerebral blood flow in the demented group was significantly lower than that of normal subjects of comparable age. However, individual values for the two groups overlapped; therefore these values are not as adequate for discriminating as the bilateral $CMRO_2$. The unilateral cerebral blood flow showed even greater scatter. Similar arguments also apply to the cerebral vascular resistance. Increased resistance was found both in cases considered to have cerebral vascular disease and in cases without cerebral vascular disease. The 10 demented patients all had normal oxygen saturation of the cerebral venous blood, with an average of 56%, presumably indicating normal cortical oxygen tension.

The vascular reactivity to CO_2 was estimated for all demented patients by measuring the cerebral venous oxygen saturation following the inhalation of 7% CO_2 for two to three minutes. An average venous oxygen saturation of 77% was found after CO_2, as compared with 74% in 10 normal patients of comparable age. The percentage rise in mean arterial blood pressure was approximately 20% in both groups. Those of the demented patients in whom the cerebral disease was on clinical evidence assumed to be secondary to cerebral vascular disease showed the same response to CO_2 as those in whom cerebral vascular disease was not suggested by the clinical data.

Studies of the vascular reactivity to CO_2 in subjects with cerebral arteriosclerosis have been carried out previously,[8,9] and a diminished reactivity was found on comparing groups of the same average age. However, it was not possible to disclose cerebral arteriosclerosis in the individual,—a finding that agrees with the results for the present group of patients. The vascular origin of organic dementia in elderly patients with retinal arteriosclerosis who have never had a stroke is as yet not well founded, and the etiology of dementia suggested by the

diagnoses given in the case histories must be treated with considerable reservation in several cases.

Comment

Neurophysiologic Data. — A correlation between mental function and cerebral oxygen consumption was noted by Kety,[10] who stated:

> In all of our studies we have been impressed with the close correlation between the level of consciousness and the rate of oxygen consumption by the brain. In patients who are comatose for whatever reason, cerebral oxygen consumption falls to a value of less than 2.0 cc. per 100 Gm. per minute, while in those who are semistuperous or confused, the value lies between 2.5 and 3.0.

A similar correlation had previously been suggested by several other workers.[11-15] Kety's results have been supported by numerous reports during the last few years,[16-19] with the only modification that $CMRO_2$ values below 2.0 have been found in severe cases of organic dementia without loss of consciousness.[20]

All these recent studies employed the inert-gas diffusion technique of Kety and Schmidt [21] without important modifications, as they all used unilateral internal jugular blood as representative of cerebral venous blood and nitrous oxide as the inert gas. In these studies the normal and the pathological groups overlapped to some extent with regard to $CMRO_2$ values (unilaterally determined), the lowered values of demented patients being evident only when the groups were compared statistically. Using the present modification, the correlation of bilateral $CMRO_2$ and mental function was close in each individual case.

The low $CMRO_2$ in organic dementia may be interpreted as follows: The gray matter, of which the cerebral cortex forms the bulk, has the highest oxygen consumption of the quantitatively important tissues from which venous blood is obtained. Thus, a subnormal $CMRO_2$—3.0 cc/100 gm/min. or below [2]—means that 100 gm. of brain tissue contains less cortex than normally and/or that the cortex consumes less oxygen than normally (the nature of the method is such that the weight of the brain does not influence the result). The low $CMRO_2$ values found in all cases of unquestionable dementia studied in this paper demonstrate the presence of and quantify extensive cortical hypofunction in the single case. Judged from the clinical data, this cortical hypofunction was presumably chronic and mainly irreversible; i. e., it was presumably caused by lesions which pathoanatomically might be described as cortical atrophic lesions: Cortical atrophy was presumably the cause of the low $CMRO_2$ in these patients. The air encephalographic studies tend to confirm this conclusion, as cortical atrophy was found in the five demented patients so examined.

Psychological Data. — Slight degrees of cerebral hypofunction are usually difficult to diagnose psychologically. However, the block-pattern test and fluctuations in digit learning appear to offer possibilities for ascertaining mild hypofunction in the individual case and on an objective basis.

Fluctuations in Digit Learning: Abnormal fluctuations in performance have long been known to occur in organic dementia,[22-25] but have not been much used diagnostically. They were considered suitable for use in the present study because they could be defined almost irrespectively of the level of performance per se, and thus relatively independently of the patient's previous education and experience.

That the fluctuations in digit learning as defined here are abnormal under optimal conditions seems acceptable from a psychological viewpoint because of their size (at least four repetitions, often more).

The nature of the task, together with the standard conditions, means that normal fatigue and momentary extraneous distractions may be regarded as improbable causes. Furthermore, the patients were unable to give any explanation of the alterations in their performance; they reported that they had been consistently exerting every effort in their work, had not been distracted, and had not adopted varying learning procedures. The fluctuations could, therefore, be

referred to cerebral hypofunction, other psychopathological states having been excluded.

As learning processes are well known to be easily affected by cerebral hypofunction, it was considered that abnormal fluctuations during learning would provide an early sign of slight organic dementia. This assumption has been borne out by the results obtained.

As the fluctuations in learning terminate at a $CMRO_2$ of 2.6, one may provisionally interpret them as indicating an intermediate stage between normal learning and a degree of mental incapacity obviating even brief, comparatively normal learning performances. Near the normal $CMRO_2$, fluctuations in digit learning appear to be analogous to the severe blocking phenomena occurring in hypoxemic normal persons in the course of otherwise normal performances.[26]

This interpretation implies that lack of fluctuations in digit learning in cases of organic dementia points to relatively severe mental incapacity. This has hitherto been confirmed by the fact that when fluctuations in digit learning were not present in the abnormal group, there were gross, seemingly unremitting disturbances of retention and/or learning. Such disturbances were manifested clinically, on psychological tests of learning, and by the patients' inability to learn from their work on higher stages of the block-pattern test.

However, fluctuations are not easy to work with, as they do not always appear in the course of the comparatively brief digit-learning test, although present in other learning tasks (Table, Case 8). Furthermore, stringent controls are necessary if the fluctuations are to be causally interpreted in an unequivocal manner. A more practical symptom of mild cerebral hypofunction in this latter respect is inability to build the Wechsler or similar block patterns from the original drawing without aid.

With regard to mildly deficient abstract behavior, as instanced by this criterion, Nadel [27] has shown that block-pattern tasks are rarely difficult for clinically normal persons, whereas one commonly finds difficulties in persons with organic dementia. Goldstein and Scheerer [7] were of the opinion that a patient was normal provided he could build their patterns correctly on returning to the original, as he thereby demonstrated that he had learned from his work.

It must be pointed out in this respect that the standard procedure suggested by these authors demands that Stage I be presented immediately after the correct completion of the model at a higher stage. Possibly, owing to the block construction functioning as a brief presentation of Stage V, patients whose immediate retention is not seriously impaired have been observed to work efficiently, though concretely, under these conditions. They are, nevertheless, unable to repeat the performance after the lapse of a few minutes. To be regarded as having learned in a normal manner, the patient should be able to manage repeat tests on Stage I at the close of the test or the next day.

Using Wechsler's [5] patterns, the present study suggests that inability to build one or more of them immediately from the original drawing indicates hypofunction (Cf. $CMRO_2$ values in Table) if the test is given under the standard conditions described above. This finding is confirmed psychologically by the fact that such patients also manifest pathological fluctuations during digit learning. Goldstein and Scheerer's criterion, on the other hand, applies more to severer cases of organic dementia.

Summary

Clinical, neurophysiological, and psychological data were obtained and evaluated individually for 19 subjects. Clinically, 6 were normal; 3 had questionable dementia, and 10, indisputable dementia.

The cerebral metabolic rate of oxygen ($CMRO_2$) was measured in cubic centimeters of O_2 per 100 gm. of brain per minute by the Kr^{85} method, using bilateral sampling of internal jugular venous blood. The clinically normal group had a $CMRO_2$

of 3.6-3.2; the intermediate group, a $CMRO_2$ of 3.2-3.0, and the demented group, a $CMRO_2$ of 2.8-1.6.

Arguments are advanced that abnormally low $CMRO_2$ (3.0 or below) in patients without acute cerebral affections indicates cortical atrophy—a conclusion confirmed by air encephalography for the five subjects so examined.

The psychological grouping of the patients was based on the presence or absence of fluctuations during learning and on two criteria derived from a block-pattern test. The four groups thus obtained comprised one without abnormalities, and three of increasing mental dysfunction. These groups correlated well with the $CMRO_2$ values in all cases.

Observations for the six patients with $CMRO_2$ values of 3.0 to 2.6 suggest that the psychological method described offers possibilities for the diagnosis of slight organic dementia.

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Flicker Fusion Thresholds in Multiple Sclerosis

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Problem

The visual flicker-fusion threshold (FFT)* has been reported to be lower in patients with brain damage than in persons free from such pathology.[1-6] Most of these studies have been concerned with the effects of damage to the gray matter of the brain, especially to the frontal and occipital lobes, and the relationship of this damage to FFT. The present study is concerned with a comparison of FFT's of patients with multiple sclerosis (M. S.), a disease which involves the white matter or fiber tracts, and patients without central nervous system disorder.

Multiple or disseminated sclerosis is one of the demyelinating diseases, characterized by a multiplicity of sensory and motor symptoms. At the pathological level, the presence of demyelinated glial patches (acute, subacute, and chronic lesions scattered throughout the cerebrum, brain stem, and spinal cord) and other areas of actual axon destruction leaves no doubt as to the organic changes in the central nervous system of M. S. patients.[7,8] While these lesions are found mainly in the white matter, they may be present in the gray matter also. At the clinical level, disturbances in affect and mentation sometimes occur which resemble symptoms seen in other organic conditions.

The fact that flicker discrimination has been found to be impaired in various pathological conditions of the central nervous system, e. g., those due to toxins and anoxia, in addition to actual damage to brain tissue,[1,3] leads to the inference that states which tend to interfere with normal brain functioning should result in an impaired flicker discrimination. On the basis of the cortical neural pathology associated with multiple sclerosis, it is predicted (*a*) that M. S. patients will have a lower FFT (i. e., be less sensitive to flicker) than controls and (*b*) that the impairment of flicker sensitivity will parallel the severity of the disorder within the M. S. group.

It is important to note that one crucial variable must be controlled, i. e., impairment of vision due to lesions of the optic nerve. The M. S. patient is often subject to retrobulbar neuritis, with consequent visual impairment. While this may be severe at first, acuity almost always improves rapidly. However, after repeated attacks, or severer lesions, atrophy of the optic fibers may occur, especially the maculopapillar bundle involved in central vision.[7,8] Since the technique employed in this experiment determines central flicker-fusion thresholds, such controls are important. Two measures of such difficulty may be obtained: (*a*) the visual field examination for scotomata and (*b*) an examination of the fundi for pallor which is often associated with optic nerve degeneration.

Methods and Materials

Subjects.—Twenty male patients with definite diagnoses of multiple sclerosis were obtained from

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* The rate, in cycles per second, of successive light flashes from a stationary light source at which the sensation of flicker disappears and the light becomes "steady." A "lower" threshold indicates poorer discrimination.

two VA general hospitals.† All M. S. subjects were enrolled in a larger cooperative study of the disease conducted by a number of VA hospitals. The duration of the disease in this group of patients ranged from 1 to 24 years, with an average of 8.7 years. The control subjects were 20 male medical and surgical patients with no evidence of central nervous system disorder; these subjects were part of another study investigating the relationship between flicker-fusion thresholds and certain personality variables, but were tested under the same conditions on the same apparatus.‡

Criteria for the selection of both groups included (*a*) no severe psychiatric disturbance, (*b*) no smoking for at least 15 minutes prior to the test, and (*c*) no intake of drugs known to alter FFT.

TABLE 1.—*Age, Education, and Duration of Multiple Sclerosis in Control and Multiple Sclerosis Groups*

Groups	Age		Years of Schooling		Duration of M.S., Yrs.	
	Mean	Range	Mean	Range	Mean	Range
Multiple sclerosis	35.7*	23-60	11.0	3-16	8.7	1-24
Control	28.3	20-41	10.7	3-16	...	...

* A U-Test indicates that the M.S. group is significantly older ($P<0.01$) than the control group.

Pertinent data for both groups of subjects is presented in Table 1. The M. S. group is significantly older than the control group ($P<0.01$), a finding which will be discussed later. No difference was found between the two groups in educational level.

Apparatus.—The equipment consisted of a stable, noiseless electronic apparatus which provided a moderately low-intensity flickering light. Subjects were asked to look at a test patch 5 mm. in diameter mounted at eye level, 30 cm. from their eyes. Binocular fixation was used, and control of the head position was maintained with aid of a chin rest. The room was dimly lighted by a 40-watt recess light; the target patch was illuminated by a Sylvania Electric Glow Modulator tube (R1131C). This light source was activated by an electronic unit, which provided an input to the tube of essentially square-wave form. The brightness of the patch was 1.09 milliamberts, as determined by a Macbeth Illuminometer. Flicker rates could be varied from 10 to 60 cycles per second (cps) with the light-dark ratio fixed at 60:40 over the entire range. The intertrial period was approximately two seconds. The exposure time for each stimulus presentation was 1.5 seconds. Flicker rates were reliable within one-half cycle or less.

Procedure.—The subject was seated facing the flicker apparatus and allowed to adapt to the dimmed light for approximately three minutes. After this, he placed his head on the chin rest, was given instructions, and was presented with a flickering light (20 or 10 cps) and a steady light (60 cps as examples. After clarification of questions, the stimuli were presented by the method-of-limits procedure, in 0.5-cycle steps.

Ten runs, five ascending runs and five descending runs, constituted Trial I. This was considered practice. After a 30-second rest, the experimental series was introduced. This series consisted of two trials of 10 runs each (Trials II and III) separated by a 30-second rest period. Other conditions of administration were identical with those in the first trial.

Threshold determinations were made before therapy was instituted.

Other Measures.—Routine visual field examinations were obtained on the M. S. patients. Conditions such as an enlarged blind spot and the presence and location of scotomata were noted. Fundus examinations were reported as to the presence and location of pallor.§ No active cases of retrobulbar neuritis were reported. The control subjects did not manifest any serious uncorrected visual defects.

In order to determine the severity of multiple sclerosis, the Bronx Scale[10] was employed. Ratings on this scale are in terms of the degree of incapacity of the patient and thus reflect indirectly and imperfectly the severity of the disorder. It is an 11-point (0-10) scale, ranging from "normal," at the lower end, through "assistance required for walking," in the middle, to "death from M. S.," at the upper end. Ratings of the M. S. patients were made by experienced neurologists before the course of therapy was instituted. The average rating was 5.6, with a range of 2 to 7.

Treatment of the Data.—The flicker-fusion data in terms of the percentage flicker reported at each half-cycle-step interval were plotted on normal-

† Dr. William Harris, Chief Psychologist, VA Hospital, Richmond, Va., aided in procuring additional multiple sclerosis patients.

‡ Dr. Ora Jones, formerly of the VA Hospital, Durham, conducted the experimentation with the normal group as part of another study.*

§ Dr. Albert Heyman, Chief of the neurology service, performed these examinations, as well as the Bronx Scale ratings.

TABLE 2.—*Means and Standard Deviations of Flicker-Fusion Threshold Values for Multiple Sclerosis and Control Groups, Trials II and III*

Group	Mean, Cps	S.D., Cps
M.S.	29.77*	7.33
Control	40.23	2.16

* A U-Test indicates that the threshold values for the M.S. group are significantly lower than those for the controls ($P<0.001$).

probability paper on the assumption that the distributions were normal. The straight line, assumed to characterize the distribution, was then fitted visually.‖ The threshold was defined as that frequency with which the subject reported flicker 50% of the time.

All comparisons between groups were made by the Mann-Whitney U-Test,[11] a nonparametric technique. Analyses within groups were made by the Wilcoxon Paired Replicates *t*-Test[11] or by rank correlational procedures. The use of nonparametric techniques was necessary because of the lack of homogeneity of the variances.

Results

The mean FFT on Trials II and III for the M. S. group was 29.77 cps, 10.46 cps lower (i. e., less sensitive) than that for the controls, a difference significant at the $P<0.001$ level (Table 2). However, before these results can be interpreted, the relationship between FFT and other variables must be examined.

The fact that the controls are significantly younger than the M. S. group cannot explain the pronounced difference obtained, since in this age range Misiak[12] has shown that age and FFT are minimally related. Further, a comparison of M. S. patients and controls who were matched for age gave rise to the same marked difference in thresholds.

‖ Dr. Robert Wagoner, Duke University, aided us in this phase of the study.

Another possible explanation for the obtained differences might be that the M. S. patients, by virtue of their chronic disease, were more easily fatigued, leading to a decline in sensitivity. Pertinent to this point is a comparison of threshold values for Trial I and Trial III in both groups, presented in Table 3. Both M. S. and control groups show a slightly decreased sensitivity in that the mean values for Trial III are lower than those for Trial I. However, it is equally clear that the impaired FFT of the M. S. group is as marked on Trial I as on Trial III.

Results of the visual field examination revealed that only three of the M. S. group had field defects. In two a slight constriction of the visual field was apparent; the third had an enlarged blind spot in one eye. However, 9 patients out of 20 had some degree of optic pallor, chiefly bitemporal. In Table 4 a comparison is presented of the FFT values for the Pallor group (FFT=24.70 cps), the Non-pallor group (FFT=33.91 cps), and the control group (FFT=40.23 cps). All three groups are significantly different from one another on the $P<0.01$ or greater level.

The relationship between the FFT's of the M. S. patients and their ratings on the Bronx Scale was not significant (ρ of -33; $P>0.05$), although in the predicted

TABLE 3.—*Flicker-Fusion Threshold Means and Differences Between Means for Trials I and III for Multiple Sclerosis (M. S.) and Control Groups*

	Trial I Mean, Cps	Trial III Mean, Cps	Differences Between Means	P*
M.S.	29.84	29.74	0.10	N.S.
Control	41.20	40.10	1.10	<0.02>0.01
Difference between means	11.36	10.36		
P†	<0.001	<0.001		

* *P* value established by Wilcoxon's Paired Replicates *t*-Test.
† *P* value obtained by U-Test.

direction. The lack of significance is not surprising in view of the restricted range of scoring on the Bronx Scale. It seems likely that with a greater range of ratings the correlation might attain statistical significance.

TABLE 4.—*Comparison of FFT Values in "Pallor" and "Nonpallor" Multiple Sclerosis and Control Groups of Patients*

Group	Mean (cps)*	S.D. (cps)
Multiple Sclerosis		
Pallor (N=9)	24.70	5.29
Nonpallor (N=11)	33.91	6.15
Control (N=20)	40.23	2.16

* U-Test indicates that the three groups differ significantly from one another, at least at the $P < 0.01$ level.

Comment

The marked difference in flicker-fusion thresholds found in this experiment confirms the results reported by Ross and Reitan.[13] These investigators noted a significant depression of FFT in 13 M. S. patients who were closely matched with a nonorganically impaired group of patients. They interpret their results as support for the "central" hypothesis of flicker discrimination, i. e., that reduced efficiency of brain functioning leads to an impairment at the central perceptual-discriminative level. This interpretation does not take into consideration the known optic neuropathy which exists in many cases of multiple sclerosis. For example, Gartner,[14] using histopathological techniques, found degeneration in the optic nerve in 10 out of the 10 M. S. cases.

As Landis[15] has pointed out, the size of the retinal area stimulated (and thus the number of fibers excited) has a direct bearing on the threshold obtained. If the number of active fibers is reduced, then, in accordance with the Granit-Harper Law, an impairment in flicker-fusion discrimination may be expected.

The importance of this point in interpreting the present data is heightened by a recent experiment. Kurachi and Yonemura[16] found a pronounced loss of flicker sensitivity in patients who had scotomata as a result of retrobulbar neuritis. Increasing the target size within the bounds of the field subtended by the scotomata did not produce any change in FFT. However, when the target was large enough to cover an area greater than the scotomata, the usual logarithmic relationship between FFT and the area stimulated was produced. While the slopes for the latter were similar to those found in normal eyes, the actual FFT's were lower than the normal at each point.

However, the presence of scotomata in the present experiment was noted only in three patients and could hardly account for the pronounced differences. On the other hand, the breakdown of the group into "Pallor" and "Nonpallor" subgroups indicated that the Pallor group was markedly impaired in flicker discrimination. The usual interpretation of a pale nerve head is that some optic nerve degeneration has occurred, although pale nerve heads can be found in normal eyes.[7,8] If the usual interpretation is accepted, and indeed the results of this experiment are in accord with such an interpretation, the question arises why more defects in the visual field were not found. The answer seems to be that the standard visual field perimetry examination is not sensitive enough to reveal defects of the type associated with multiple sclerosis, especially when the acute phase of retrobulbar neuritis has passed, as in the patients in this study. Miles[4] has published data in support of this. In plotting the visual fields of nine M. S. patients, using a flicker perimetry method, he found visual field defects which were not detected in the standard examination. In the acute phase of retrobulbar neuritis both flicker and standard fields were found to be depressed. After two months the standard fields became normal, while the flicker fields remained depressed for six months before they began to improve. In no case, however, did the flicker fields return completely to normal. These studies in conjunction with the present findings suggest that a "central" ex-

planation of the lowered FFT in M. S. patients can only be invoked when control is established over the "peripheral" variable of optic neuropathy. To the extent that the control, i. e., the presence of optic pallor, instituted in this study is an adequate one, the finding that the nonpallor patients have significantly lower thresholds than the controls might serve to bolster the explanation of an impairment of discrimination at the central level in multiple sclerosis. This would be in accord with the marked similarity in functioning on the Halstead battery of tests found among M. S., control, and organic disease patients by Ross and Reitan.[13]

Finally, the potential usefulness of the flicker-fusion threshold as a diagnostic adjunct may be emphasized. A comparison of the individual FFT's in the two groups (Table 5) reveals that only 4 of the 20 M. S.

TABLE 5.—*Flicker-Fusion Threshold Values for Multiple Sclerosis and Control Subjects**

Subject No.	Controls, Cps	M.S., Cps
1	44.8	40.7
2	44.0	39.2
3	42.5	38.5
4	42.0	38.2
5	41.7	37.6
6	41.6	34.9 P†
7	41.0	34.2
8	40.7	34.1
9	40.6	33.1
10	40.5	31.4 P
11	40.4	30.6
12	39.7	27.9
13	39.3	25.9 P
14	39.0	25.5 P
15	38.8	21.9 P
16	38.3	21.2 P
17	37.8	21.0 P
18	37.6	20.5 P
19	37.2	20.1 P
20	37.1	19.5 P

* The values above the bold face line indicate the number of M.S. patients (four) who fall in the range of the controls. The values below the light-face line refer to the number of controls (13) who fall in the range of the M.S. patients.
† *P* indicates Pallor group.

patients have a FFT within the range of the controls. All M. S. subjects where pallor was noted had values below the range of the control group. For the neurologist faced with the notoriously difficult task of diagnosing multiple sclerosis, especially in its early stages, demonstration of reduced flicker sensitivity may provide the additional evidence for a positive diagnosis.

Summary

The central visual flicker-fusion thresholds of 20 male veteran patients with multiple sclerosis and 20 control subjects, with no central nervous system disorder, are compared. A markedly impaired flicker discrimination is found in the M. S. group. Only three M. S. patients had evidence of scotomata; however, nine possessed some degree of optic pallor. The pallor group manifests the greatest impairment of flicker discrimination, but the nonpallor M. S. group shows also significantly lower values than the controls. It is suggested that these results are due mainly to optic neuropathy accompanying retrobulbar neuritis. These effects apparently are not revealed by standard visual field examinations but do appear when flicker-fusion thresholds are determined.

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Trimethadione: Its Dosage and Toxicity

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In the decade during which trimethadione (Tridione) has been in wide clinical use it has proved to be an excellent therapeutic agent for the treatment of the petit mal triad. The petit mal triad is manifested by episodes of absence, akinesis, and myoclonic jerks (occurring singly or together in a given patient), with the electroencephalogram showing characteristic 3-per-second spike-and-wave discharges, bilaterally symmetrical and most prominent anteriorly. It is proposed that its therapeutic usefulness can be successfully and materially extended by the vigorous usage of this medication in doses considerably higher than those generally employed. The following three cases illustrate its effectiveness when used in this manner.

Report of Cases

CASE 1.*—Twenty-year-old youth; weight, 55.7 kg. (122.5 lb.).

Nothing is known of the patient's birth and early development. He began having seizures at about the age of 5 or 6 years. He had no warning or aura. Seizure types: 1. The majority of the seizures consisted of a brief loss of contact with the environment lasting less than a minute, accompanied by nodding of the head, blinking of the eyes, and swaying of the trunk. He generally did not fall with such attacks. Following such an episode, he felt somewhat confused and dazed for a few seconds. 2. Less frequently he had attacks in which he would abruptly fall to the floor without warning and remain unconscious for 30 to 40 minutes. He had been told that there were shaking movements of the extremities with these episodes, but tongue biting and incontinence did not occur. On admission to the Clinical Center of the National Institutes of Health, the patient was having an average of 20-40 seizures of the first type daily (with occasionally as many as 80 to 100 in a single day) and about 1 of the second type every two weeks.

Prior to admission the patient had been tried, with no appreciable degree of success, on the following medications (with maximal doses listed): phenobarbital 0.1 gm/day, diphenylhydantoin (Dilantin) sodium 0.5 gm/day, trimethadione (Tridione) 1.2 gm/day, methylphenylethyl hydantoin (Mesantoin) 0.4 gm/day, primidone (Mysoline) 2.25 gm/day, glutamic acid 2.4 gm/day, and phensuximide (Milontin) 2.0 gm/day. The following combinations are known to have proved ineffective; phenobarbital 60 mg/day and diphenylhydantoin sodium 0.4 gm/day; phenobarbital 60 mg/day and trimethadione 0.9 gm/day; diphenylhydantoin sodium 0.5 gm/day, methylphenylethyl hydantoin 0.4 gm/day, and phenobarbital 0.1 gm/day; primidone 1.0 gm/day, trimethadione 1.2 gm/day, diphenylhydantoin sodium 0.4 gm/day, and glutamic acid 2.4 gm/day; primidone 1.5 gm/day, phensuximide 1.0 gm/day, and phenobarbital 0.09 gm/day. Personality problems, in the form of temper tantrums, irritability, and occasionally hostility and destructiveness, had occurred with periods of especially severe seizure activity.

On admission, the patient was well developed, well nourished, alert, and cooperative. General physical examination revealed no significant abnormalities. He had nystagmus on lateral gaze and showed minimal generalized slowness of both motor and mental activity. Psychological examinations revealed him to be of slightly below average intellectual abilities.

Chest and skull x-rays were interpreted as normal. Hemoglobin and hematocrit were normal. White blood cell count varied from 3600 to 6700 per cubic millimeter (with most counts between 4000 and 5000 per cubic millimeter). Differential counts were consistently within normal limits, with 60%-65% neutrophils. Serial urinalyses revealed no abnormalities. Fasting blood sugar, serum electrolytes, liver function, and blood urea nitrogen were consistently within the range of normal.

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* Dr. Leonard Berg permitted the report of this case and made many helpful suggestions concerning the preparation of this manuscript.

Electroencephalograms revealed (1) poorly regulated background activity with mixed frequencies of moderate amplitude, the dominant rhythm being 7 per second; (2) bursts of 3-per-second wave-and-spike activity of high amplitude, maximal anteriorly, and (3) sensitivity to hyperventilation. The impression was that the electroencephalograms showed "disturbances typical of centrencephalic epilepsy."

At the time of admission the patient was receiving phenobarbital 90 mg/day, primidone 1.5 gm/day, and phensuximide 1.0 gm/day. On this regimen he was having 40-60 seizures of the first type daily.

Following a control period of three weeks the patient was tried on L-asparagine in doses up to 120 gm/day, without significant effect on the seizures. Primidone and phenobarbital were discontinued, and the patient continued to have approximately 50 minor seizures daily during the first three months of hospitalization. He was started on trimethadione 1.8 gm/day, and this amount was gradually increased to 3.6 gm/day (in divided doses) during the ensuing month. His seizures were reduced to approximately 20-30 per day with this regimen, and he appeared to show a definite improvement in his mental alertness. L-asparagine was discontinued. The trimethadione was increased to 4.2 gm/day, and seizures decreased to less than 10 per day. His psychological improvement was striking. On this dose, there was a further decrease in the seizure frequency to complete disappearance of the minor seizures during the next month. He had one major seizure, and diphenylhydantoin 0.3 gm/day was added as prophylaxis.

Because of minimal blurring of vision and discomfort in bright light, the trimethadione was reduced to 3.6 gm/day. The patient remained seizure-free and at the time of discharge had had no attack for six weeks. He has been followed in the outpatient department in the 17 months since discharge, and during this time he has had no minor seizures and only one major seizure (11 months after discharge). Trimethadione has been gradually reduced to 2.4 gm/day, and he continues to take diphenylhydantoin sodium, 0.3 gm/day.

With the clinical improvement in the seizures, there was a concomitant improvement in the electroencephalogram. As the seizures became less frequent, a basic 8-per-second alpha rhythm appeared. For several months following the clinical disappearance of seizures the EEG continued to show rare discharges of the multiple spike-and-wave type, not being organized into the typical 3-per-second bursts, however. At the time of the last study, when he had been seizure-free for approximately 16 months, the electroencephalogram revealed a well-developed 8-9-per-second alpha rhythm. A few irregularities were noted, but no paroxysmal discharges were seen either at rest or with hyperventilation. The record was interpreted as being "borderline abnormal."

The patient's photophobia gradually disappeared over several months after his discharge. Frequent examinations of the blood were done, and his white blood cell count generally remained from 4000-5000 before and after trimethadione, and the differential count remained normal (Fig. 1).

CASE 2.—Nineteen-year-old youth; weight, 70 kg. (154 lb.).

Birth and early development were normal in this patient. The seizures began at 7 years of age and consisted of brief episodes of loss of contact with his environment, with staring or blinking of the eyelids, sometimes accompanied by head nodding and symmetrical jerks of the upper extremities. At the age of 14 years he began to have rare generalized convulsions, characterized by prolonged loss of consciousness, clonic movements of all extremities, chewing motions of the mouth, and tongue biting. At the time of his admission to the Clinical Center, the patient was having approximately 20 to 40 minor seizures daily. The major seizures were occurring once or twice yearly.

Prior to admission the patient had been tried on the following medications alone or in combination (maximum dosages given), without any effective control of his seizures: diphenylhydantoin sodium 0.45 gm/day, phenobarbital 0.25 gm/day, methobarbital (Mebaral) 0.45 gm/day, methylphenylethyl hydantoin 0.6 gm/day, trimethadione 1.8 gm/day, primidone 1.25 gm/day, benzchlorpropamide (Hibicon) 5.0 gm/day, bromide 2.7 gm/day, ephedrine, ammonium chloride, and amphetamine (Benzedrine). Details of the combinations used are not available.

On examination the patient was found to be an alert, well-developed young man of normal intelligence. No significant abnormalities were found on neurological or on general physical examination.

A pneumoencephalogram had been done elsewhere shortly before his admission and had revealed no abnormalities. Chest and skull x-rays were interpreted as normal. Urinalysis, fasting blood sugar and blood urea nitrogen determinations, and liver function studies were normal. White blood cell counts before trimethadione was begun ranged from 3900 to 5400 per cubic millimeter, with 55%-66% neutrophils. Blood electrolytes were normal except for a slightly increased carbon dioxide content.

Electroencephalograms showed (1) well-regulated and symmetrical background activity; (2) paroxysmal discharges consisting of 2.5-3-per-

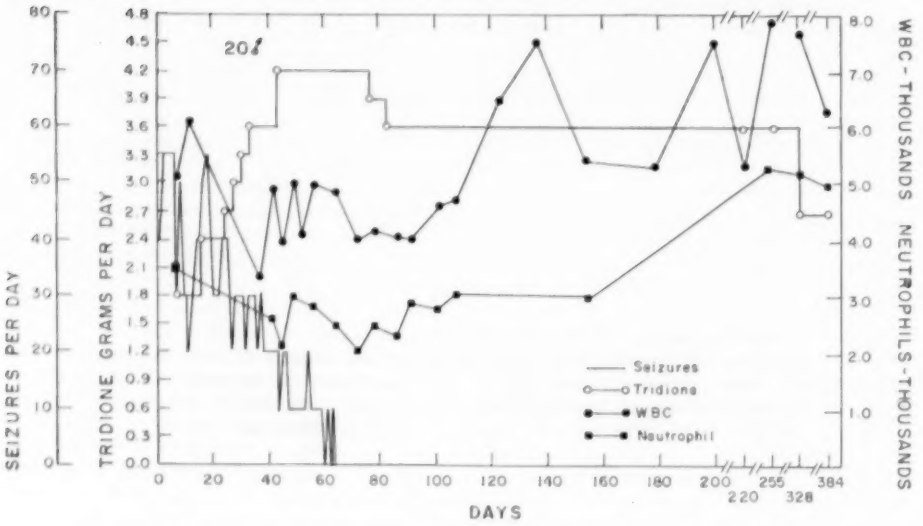

Fig. 1.—Plotting of seizure frequency, trimethadione (Tridione) dosage, white blood cell count, and total neutrophil count for Patient 1 for 384 days following institution of trimethadione therapy.

second wave-and-multiple-spike complexes of very high voltage and long duration, appearing bilaterally synchronous and symmetrical over the two hemispheres, with maximal amplitude over the frontal regions, and (3) sensitivity to hyperventilation. Impression was " a centrencephalic type of epilepsy."

Following his admission the patient was tried on acetazoleamide (Diamox) 1.0 gm/day, and L-glutamine, up to 100 gm/day, in attempts to control his seizures. Neither drug was effective, and after they were stopped he continued to have an average of 40-60 of the minor seizures daily, and occasionally as many as 80 to 90 in a single day.

The patient was then begun on trimethadione 1.2 gm/day, which was gradually increased over a 20-day period to 4.5 gm/day. When the dosage level reached 2.7 gm/day, the seizures were reduced to an average of 20-40 per day. When he was receiving 3.6 gm/day, he began to develop some lethargy and photophobia, which increased when the amount given was increased to 4.5 gm/day. At this time the patient was quite drowsy and had slurred speech, slight ataxia, hiccoughs, and difficulty in following a conversation. During this period, although no seizures were noted by observers, the patient continued to report seizures daily, which he said he "felt on the inside." Because of the development of these symptoms, the trimethadione was reduced to 3.6 gm/day, and within the week his minor seizures had disappeared entirely. The dose of trimethadione was further decreased to 3.0 gm/day, and the patient remained seizure-free for the remaining two weeks of his stay in the hospital. During this period the toxic symptoms disappeared almost completely, so that at the time of discharge he complained only of slight photophobia.

With the decrease in seizures his electroencephalogram showed comparable improvement. The last two electroencephalograms taken in the hospital revealed no epileptiform discharges at rest and none precipitated by five minutes of hyperventilation.

The patient's white blood cell count and neutrophils were carefully followed during the period of trimethadione administration. As shown in Figure 2, the white cell count varied from 2800 to 7200 during this period, and the neutrophil count varied from 1500 to 4800 per cubic millimeter, showing considerable variations within a few days' period.

The patient was discharged from the hospital taking trimethadione 3.0 gm/day, diphenylhydantoin sodium 0.2 gm/day, and mephobarbital 0.3 gm/day. At last report, approximately six months after leaving the hospital, the patient's trimethadione dosage had been successfully reduced to 1.2 gm/day. At that time he was said to be having only a brief series of minor seizures occurring once every 10 to 20 days.

CASE 3.—Seventeen-year-old youth; weight, 78.5 kg. (173 lb.).

Birth and early development were normal. At the age of 13 years the patient began to have minor seizures. These consisted of episodes of sudden

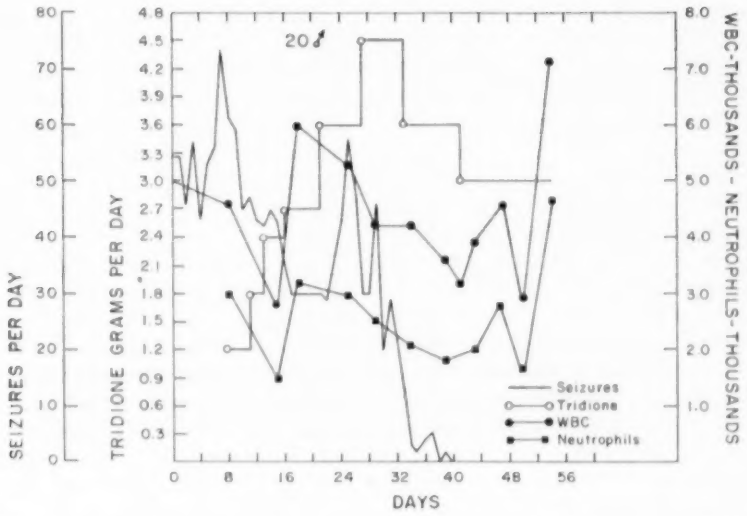

Fig. 2.—Plotting of seizure frequency, trimethadione (Tridione) dosage, white blood cell count, and total neutrophil count for Patient 2 for 56 days following institution of trimethadione therapy.

slumping to the floor with brief loss of consciousness, episodes of symmetrical jerking of the upper extremities and head nodding, and episodes of loss of contact with his environment of brief duration with blinking of the eyelids or staring. Two years later the patient began having major seizures, manifested by an outcry, falling, tonic and clonic contractions of the extremities, cyanosis, and urinary incontinence, followed by sleepiness and drowsiness. At the time of admission the patient was having frequent minor seizures, but the exact number per day was uncertain.

Prior to admission the patient had been tried on a wide variety of medications, with no effective control ever achieved. The longest period that he had been seizure-free since the onset of the disease was eight days, on one occasion. The following medications had been given (maximal doses listed): diphenylhydantoin sodium 0.3 gm/day, paramethadione 2.1 gm/day, phenobarbital 0.06 gm/day, trimethadione 0.3 gm/day, ammonium chloride 3.0 gm/day, benzchlorpropamide 2.0 gm/day, primidone 1.5 gm/day, methobarbital plus diphenylhydantoin (Mebroin) 0.75 gm/day, and *d*-amphetamine (Dexedrine) sulfate 27.5 gm/day. Combinations given had included the following: diphenylhydantoin sodium 0.2 gm/day and paramethadione 0.6 gm/day; diphenylhydantoin sodium 0.2 gm/day, phenobarbital 0.06 gm/day, and paramethadione 1.2 gm/day; diphenylhydantoin sodium 0.2 gm/day, phenobarbital 0.06 gm/day, paramethadione 1.5 gm/day, and ammonium chloride 0.5 gm/day; paramethadione 1.5 gm/day and Mebroin 0.75 gm/day; paramethadione 0.9 gm/day, Mebroin 0.45 gm/day, and primidone 1.5 gm/day. He was taking the last-named combination at the time of admission.

General physical examination was unremarkable. Neurological examination showed the patient to be somewhat lethargic and quite slow in his responses but without other specific neurologic abnormalities. Chest and skull x-rays revealed no abnormalities. Urinalysis; fasting blood sugar, blood urea nitrogen, and liver function studies, and hematologic studies were within the limits of normal. Electroencephalograms showed (1) poorly organized background activity; (2) paroxysmal discharges of high voltage 2.5-3.5-per-second spike-and-wave complexes, synchronous and maximal over the anterior head regions. The impression was "centrencephalic epilepsy."

Following admission primidone was discontinued and the patient was continued on paramethadione, diphenylhydantoin, and methobarbital. After two weeks in the hospital trimethadione was gradually substituted for paramethadione over a period of 10 days. The trimethadione dosage was then gradually increased over a six-week period to 3.0 gm/day in divided doses. The seizure frequency gradually decreased as the dosage of trimethadione was increased, though the seizures did not entirely disappear until approximately 10 days following increase of the dose of trimethadione to 3.0 gm/day. At the time of the last examination, approximately one month later, the patient remained completely seizure-free. No signs or symptoms of toxicity

have developed. The electroencephalogram at the time of the last visit revealed a better-regulated background activity and no paroxysmal discharges either at rest or with hyperventilation.

Pharmacology

In 1944 Spielman[1] first synthesized trimethadione (3,5,5-trimethyl-2,4-oxazolidinedione). He reported this new drug to possess the analgesic potency of acetylsalicylic acid and to have a "remarkably low toxicity." Within a few months Richards and Everett[2-4] reported its anticonvulsant properties. They found in experimental animals that it had a markedly antagonistic effect against the convulsant action of pentylenetetrazol (Metrazol), picrotoxin, and electric shock, but not against strychnine. Goodman and Manuel,[5] in the next year, reported that in animals residual anticonvulsant action from single doses could be noted up to 48 hours. Suter[6] has obtained some preliminary suggestion that a single dose of trimethadione offers significantly longer protection against audiogenic seizures than does a single dose of the other commonly used anticonvulsants.

In the dog, trimethadione has been shown to be demethylated to 5,5-dimethyl-2,4-oxazolidinedione.[7] In man only approximately 2.5% of a given dose of the drug is excreted unchanged in the urine within eight hours following its oral administration.[8] Butler[9] found that following intraperitoneal injection of trimethadione in the dog the plasma concentration of 5,5-dimethyl-2,4-oxazolidinedione continues to rise for many hours, highest values being reached after 48 hours. When the dimethyl derivative itself was administered, its plasma levels were found to decrease very slowly, detectable amounts being found for many days. In one man given 0.9 gm. of trimethadione daily for six days,[9] the concentration of 5,5-dimethyl-2,4-oxazolidinedione continued to rise gradually throughout this period and on the day following the discontinuance of the drug. It was still easily detected in the blood several weeks later.

Conflicting views persist as to whether the liver,[10,11] the liver, and the kidneys,[12] or none of them,[8] is important in eliminating or metabolizing the active anticonvulsant. Studies have shown that trimethadione is not concentrated in the brain in any significantly higher concentrations than in the rest of the body.[13]

Clinical Applicability

Perlstein,[14] at a meeting of the Chicago Neurological Society on Jan. 9, 1945, first reported trimethadione to be of value in the therapy of epilepsy. Other reports of its therapeutic value soon followed from Lennox,[15-18] Thorne,[19] and Erickson and associates.[20] For complete reviews of its effects in individual series of patients, the reader is referred to papers by Lennox,[17,21] Davis and Lennox,[22] Mustard and Livingston,[23] Whitty,[24] and Davies and Spillane.[25]

Following early reports of its therapeutic value, the use of trimethadione became widespread, and it has remained so, although the indications for its use have become more discrete and implicit with the publication of results in large series of patients. It is an almost unanimous opinion that trimethadione is of specific therapeutic benefit to patients suffering from one or all components of the petit mal triad—absence, akinesis, and myoclonic seizures.[14-18,20-40] Its effectiveness in reducing seizures of this triad has been reported for 80% or more of patients so treated by several authors.[16,21,22,24,25,36,38,39] Complete remission of these seizures on trimethadione therapy has been reported in as many as 28%,[16] 31%,[22] 26%,[23] and 33%[33] of individual series of patients. It has also at various times been reported to be of some value in patients with grand mal seizures,[14,17,19,24,28] and psychomotor seizures.[28,41,42] The general consensus, however, is that its clinical usefulness is inconsequential in conditions other than the petit mal triad.

Dosage

Most authors have recommended a dosage varying between a minimum of 0.3 gm/day,

in an infant, and a maximum of 2.1 gm/day, in an adult.[14,16,17,23-30,35-39,41,42-47] Others, however, have reported the occasional use of higher dosages. Thorne [19] gave up to 2.7 and 3.6 gm/day in several severely deteriorated institutionalized epileptics. Lennox [17] states that the dose on occasions may be raised to 2.7 gm/day. Perlstein [26,29] mentions giving up to 3.0 gm/day and reports that drowsiness was used as an indication for reducing the level of the medication. Gibbs [45] suggests that doses as high as 3.6 gm/day may be necessary to bring the seizures under control. Perlstein [29] has given as much as 24 gm. in a single day to a patient with tetanus without toxic effects. Van Buren [48] has given a patient 7.2 gm/day without the achievement of effective control. This patient developed photophobia, drowsiness, hiccoughs, and stumbling, which subsided when the drug was removed.

Toxicity

Widely varying assessments of the toxicity of trimethadione have been reported by different authors. Opinions range from those who found no side-effects [14] to those who found the toxic reactions to be so severe that they feel "that the danger of Tridione may outweigh its therapeutic value."[49] In the largest published series of cases in which a careful search for toxic side-reactions has been made, Lennox [21] found that among 222 patients who reported adequately 122 had symptoms which might conceivably be due to the drug.

The toxic effects may conveniently be divided into two groups—the mild and the severe reactions. The latter includes severe hematologic, cutaneous, and renal changes presumed to be due to the effects of the medication. Table 1 contains a listing of the mild reactions which have been reported and the approximate incidence of the reactions, calculated where possible from the published data.

Photophobia is the commonest mild toxic effect, having been reported by many authors.[15,16,18,21,23-28,35,38,42,44,50] It has occurred in as many as 19 of 23 patients given trimethadione [35] and was present in 31% of Lennox' series of 222 patients.[21] It is generally rare in young children and becomes a more frequent symptom in late adolescence and adult life.[16,21,44] It clears spontaneously in most patients without stopping the medication.

Skin eruptions are the second commonest toxic effect of trimethadione. The less severe skin reactions have been reported in

TABLE 1.—*Mild Symptoms and Signs of Trimethadione Toxicity*

Dizziness and vertigo	[21,24,44]
Ataxia	[24,44]
Lack of concentration	[24,44]
Nervousness	[21]
Insomnia	[21]
Confusion and stuporousness	[28]
Hallucinatory psychosis	[45]
Confusion, disorientation, and memory defects	[44]
Diplopia	[21,44]
Blurring of vision	[27,45]
Paracentral scotoma	[24]
Pain in eyeball	[21]
Difficulty in focusing eyes	[21]
Dilated pupils	[24]
Temporary papilledema	[28]
Decreased day vision	[29]
Macropsia	[29]
Photophobia, 29.4%	[15,16,18,21,23,24,25,26,27,28,42,44,50]
Skin rashes, 9.0%	[15,16,17,18,22,24,26,46,48]
Irritability, restlessness, difficult behavior, 8.1%	[16,21,24,26,34,50,51]
Nausea and epigastric distress, 6.7%	[15,21,23,26,50,51]
Fatigue, 6.1%	[21,24,46,48]
Sleepiness and drowsiness, 4.7%	[16,21,24,26,27,28,31,48]
Hiccough, 1.2%	[21,26,34]
Sneezing	[21,51]
Headaches	[24,51]
Transient sore throat	[51]
Nosebleed	[21]
"Poor circulation"	[21]
Muscle pains in extremities	[51]
Muscular instability	[21]
Anorexia	[24]
Transient albuminuria	[24]
Generalized swelling of joints with pain and fever	[44]

as many as 20% of patients taking trimethadione.[24] Fourteen per cent of Lennox' patients [21] developed skin eruptions. These are more frequent in young children than in adults. The rash has been described as morbilliform,[27,38,44] urticarial,[24,25,35] acneiform,[24] and macular [24] and as resembling angioneurotic edema.[39] The severer cutaneous manifestations will be discussed subsequently.

Psychic effects have been reported by several authors. These have ranged from irritability, increased activity, excitability, and behavior problems [18,21,24,28,35] to confusion and stuporousness,[28] panic feelings,[39] confusion, disorientation, and memory defects,[50] and hallucinatory psychosis.[50]

Other mild reactions which have been reported are listed in Table 1.

More important are the serious side-effects of severe cutaneous, renal, and hematopoietic system involvement. In Table 2 the significant factors in the cases of severe cutaneous manifestations of trimethadione toxicity are listed, as collected from the literature where sufficient information was given. In these 15 cases the ages ranged from 6½ to 69 years, with eight females and six males (one not listed). Dosage, where given, varied from 0.24 to 1.8 gm/day. Twelve of the fifteen patients had taken the drug one month or less before the rash appeared. All but one patient eventually recovered. Full details of this fatal case [52,53] (Case 6) were never reported. Nevertheless, one patient remained blind as a result of severe corneal involvement.[54]

Table 3 lists those reports of serious renal responses, i. e., nephrosis, which we have been able to collect. The ages of the patients varied from 14 months to 24 years, with five males and four females included. Dosage of trimethadione ranged from 0.3 to 1.5 gm/day. In contrast to patients exhibiting the severe skin reactions, all of these patients but three had been receiving the drug for at least eight and a half months. The most consistent clinical manifestation was edema. Laboratory examinations showed albuminuria, decreased serum albumin, and hypercholesteremia. A few casts (granular and hyaline) were noted in two patients,[49,59] and an occasional WBC was noted in the urine of one.[63] Blood urea nitrogen was elevated in four,[49,60,61,65] and urea clearance was impaired in one.[61] Recovery occurred in all but two cases after the drug was stopped (in Case 21 the follow-up period was too short to assess the final outcome). In the cases in which death did occur [49,60] (Cases 17 and 19) one can only wonder with Lennox [66] "whether the medication or the method of administering it was most at fault," since in both these patients the trimethadione was continued after the development of nephrosis was known.

Millichap and Kirman [67] gave 12 boys, aged 8 to 14 years, 1.5 gm. of trimethadione a day and examined their urine carefully for eight weeks. In eight of these patients signs of glomerular damage were discovered within the eight weeks. Proteinuria occurred in one; microscopic hematuria, in five, and granular casts, in five. Red cells and granular casts were present in the urine of two patients seven weeks after the withdrawal of trimethadione. Whitty [24] reported transient albuminuria in a single patient. Olhagen and Svanborg [68] have attempted to produce nephrosis by administering large doses of trimethadione to rabbits. In their first animals they were able to produce hyperlipemia and mild proteinuria, but after a noticeable change in their commercially prepared trimethadione, they were unable to produce this effect in any further animals.

By far the most serious toxic effects of therapy with trimethadione are its effects on the hematopoietic system. Abbott and Schwab,[69] in discussing these effects, considered that a patient taking trimethadione would generally fall into one of three groups—those showing a modified normal response, those with a controlled neutropenia, and those with a "runaway" cytopenia. Patients in the first group would show only a change in the differential count with a reduction in neutrophils and mono-

TABLE 2.—*Factors in Cases of Cutaneous Manifestations in Trimethadione Therapy*

Case No.	Author	Age, Yr.	Sex	Type Seizure	Dosage, Gm./Day	Duration	Type Rash	Result
1	Thorne[14]	30	F	Natal trauma with epilepsy and mental deterioration	1.8	28 days	Facial edema, stomatitis, maculopapular vesicular dermatitis	Recovery
2	Pollock[11]	30	F	.....	0.9	1 wk.	Generalized papular eruption, progressing to exfoliation	Recovery
3	Pollock[11]	35	M	.....	0.9	17 days	Generalized macular, papular, vesicular eruption with hemorrhagic ulcerations	Recovery
4	Pollock[11]	34	F	.....	0.9	Approx. 1 mo.	Multiform, punctiform, maculopapular eruption on scarlatiniform base	Recovery
5	Goodman et al.[11]	--	--	.....	--	Shortly after beginning trimethadione	Severe dermatitis	Recovery
6	Kerlin[11,13]	9	F	.....	--	4 wk.	Exfoliative dermatitis	Death
7	Shaffer and Morris[11]	6½	M	General retardation of mental development and petit mal	0.6	16 days	Full-blown Stevens-Johnson syndrome	Recovery, with residual blindness
8	Briggs and Emery[11]	11	F	"Attacks"	0.6	3 wk.	Urticaria	Recovery
9	Davies and Spillane[11]	8	M	Grandmal and simple petit mal	Not over 1.5	14 days	Urticaria with erythema and desquamation	Recovery
10	Davies and Spillane[11]	26	M	Grand mal, petit mal, akinetic, myoclonic	Not over 1.5	17 days	Generalized pruritus, edema of face, exfoliation	Recovery
11	Davies and Spillane[11]	10	M	Simple petit mal	0.9	34 days	Acute erythema and edema of face	Recovery
12	Van Wezel[15]	34	F	Epigastric aura with choking sensation and unconsciousness	0.9	2 wk.	Giant urticaria; macular rash with purpura and exfoliation	Recovery
13	Leard et al.[10]	69	M	Major and minor, beginning with epigastric aura	0.6	6-7 wk.	Hemorrhagic, macular, erythematous, confluent	Recovery
14	Nordlander[17]	34	F	Petit mal	0.9	3 wk.	Rubeola-like rash with erythema, progressing to exfoliation	Recovery
15	Forsey and Black[11]	26	F	Petit mal	0.24	Several mo.	Angioneurotic edema with urticaria	Recovery

TABLE 3.—*Data on Renal Manifestations in Trimethadione Therapy*

Case No.	Author	Age, Yr.	Sex	Type Seizure	Dosage, Gm/Day	Duration	Significant Laboratory Findings	Result
16	Barnett et al.[38]	16	F	Petit mal	0.9	8½ mo.	Albuminuria; serum albumin 1.8 gm./100 cc.; cholesterol 876 mg./100 cc.	Recovery
17	Briggs and Emery[41]	8	M	Petit mal	1.5	3 mo.	Albuminuria; few granular casts in urine; serum protein 4.0 gm./100 cc.; BUN 160 mg./100 cc.; cholesterol 400 mg./100 cc.	Death
18	White[39]	19	M	Postencephalitis	0.6 0.3	9 mo. 2 mo.	Albuminuria; hyaline and granular casts; NPN 32 mg./100 cc.; cholesterol 266 mg./100 cc.; A/G 2.8/1.6	Recovery
19	Fanconi et al.[44]	6	M	Petit mal and "moyen mal"; imbecility	0.9	9 mo.	Albuminuria; hyaline and granular casts; NPN 80 mg./100 cc.; A/G 2.25/2.6; cholesterol 442 mg./100 cc.	Death
20	Tegelaers and Tiddens[43]	7	M	Petit mal	..	12 mo.	BUN increased; urea clearance impaired	Recovery
21	Kelley and Panos[42]	14m.	M	....	..	..	Proteinuria	No improvement after 2 mo.
22	Nabarro and Rosenheim[45]	24	F	Petit mal	1.5	2 yr.	Albuminuria; occasional WBC in urine; BUN 30 mg./100 cc.; urea clearance normal; A/G 1.9/2.1	Recovery
23	Björn[46]	5	F	Petit mal	1.5	26 mo.	Albuminuria; cholesterol 460 mg./100 cc.; NPN normal	Recovery
24	Steffensen and Brand	8	F	Psychomotor	0.6	6 mo.	Albuminuria; hematuria; cholesterol 908 mg./100 cc.; NPN 114 mg./100 cc.; A/G 0.7/3.3	Recovery

cytes and an increase in lymphocytes and eosinophils. A patient in the second group would have a gradual decrease in the neutrophils to below 3000 per cubic millimeter. In the third group would be those with fulminating cytopenia.

Of Lennox' 222 cases, 127 were studied with regular examinations of the blood.[21, 22, 31] No significant changes were noted in the red blood cell count, hemoglobin, or platelets. In nine patients (7%) neutrophils fell to levels between 1600 and 2500 per cubic millimeter. In eight patients (6.3%) total neutrophils fell to below 1600 per cubic millimeter. No correlation was found between the occurrence of neutropenia and the age or sex of the patient, the dosage of trimethadione, or the duration of therapy with the drug. The eight patients in whom neutrophils fell to below 1600 per cubic millimeter had been taking trimethadione from 3 weeks to 20 months before these levels were reached. Twelve of the seventeen with neutropenia had had blood counts within one month prior to the onset of the neutropenia. Of the eight patients with neutrophils less than 1600 per cubic millimeter, two continued to take the drug, and subsequent counts remained above 2700 per cubic millimeter. In a third the drug was resumed without the recurrence of neutropenia. In the others the drug was withdrawn and the neutrophils promptly returned to normal values.

In a study of 42 patients, Davidoff [28] noted a drop in the white blood cell count in 24. Decreased neutrophils and increased lymphocytes were noted in 17, and decreased lymphocytes and increased neutrophils occurred in 11. He observed a monocytosis in eight. Mustard and Livingston [23] found a leukopenia in 5 of 156 patients receiving trimethadione. In all there was a moderate to severe reduction in neutrophils. White cell counts returned to normal in all but one, in whom they remained stable for 18 months at 4500 per cubic millimeter. Whitty [24] reported a sudden marked reduction in granulocytes in 2 of 26 patients treated six months or more with trimethadione. Both returned to normal within two weeks. Kaplan and associates,[36] in 30 patients, had 1 with a reduction of leukocytes from 11,400 to 7,000 with a neutropenia (12%-15%), and another with a leukocytosis (32,000) with neutropenia (16%), both of whom had a return to normal when the drug was stopped.

On the other hand, in Davies and Spillane's series [25] of 50 patients on whom blood studies were done every three weeks, no serious changes in the hematologic picture were noted. Several authors have reported an eosinophilia to occur with trimethadione.[21, 24, 25, 28, 40]

Among the hematopoietic system responses, the most serious of all the toxic reactions is severe cytopenia. Nineteen such cases in which sufficient details were given have been collected from the literature. These are listed in Table 4.

Of these 19 patients, 13 died. Ages for the entire group ranged from 6½ to 54 years; those for the group ending fatally, from 6½ to 37 years. Thirteen were females and six were males. All but five patients (two of whom died) had been receiving trimethadione 53 days or longer. The dosage of trimethadione ranged from 0.3 to 2.4 gm/day. Two patients [70, 75] (Cases 25 and 30) were also receiving hydantoins, which might also be implicated as contributory. The usual hematologic picture was of a pancytopenia—anemia, leukopenia with neutropenia, and thrombocytopenia. Thirteen of the nineteen patients showed depression of all the three blood elements (11 of the 13 who died). Two patients who died [73, 76] (Cases 28 and 31) had normal blood platelets. The others showed varying degrees of anemia and leukopenia. Death generally occurred with profound bleeding tendencies and overwhelming infections. Bone-marrow examination, where recorded, generally showed the depression which would be expected from the depression of the blood elements. In one case [72] (Case 27) the bone marrow was reported as normal, and the

TABLE 4.—*Data on Cases of Severe Cytopenia in Trimethadione Therapy*

Case No.	Author	Age, Yr.	Sex	Type Seizure	Dosage, Gm./Day	Duration	Hematologic Findings	Result
25	Harrison et al.[19]	16	F	Grand mal	0.3 (0.3 Mesantoin)	7 mo. 6 mo.	Anemia; leukopenia with neutropenia; thrombocytopenia	Death
26	Greaves[21]	25	F	Jacksonian	1.8 0.9	6 days 12 days	Leukopenia with neutropenia	Recovery
27	Mackay and Gottstein[13]	23	F	Petit mal psychomotor	0.9-1.5	10 mo.	Anemia; leukopenia with neutropenia; thrombocytopenia	Death
28	Braithwaite[17]	11	M	Petit mal	1.2	53 days	Anemia; leukopenia with neutropenia	Death
29	Carnicelli and Tedeschi[18]	19	F	Aura of flushing and tingling of face followed by amnesia	0.9	5 mo.	Anemia; leukopenia with neutropenia; thrombocytopenia	Death
30	Gayle et al.[20]	11	F	Petit mal	1.2 (hydantoin)	4½ mo. 12 mo.	Anemia; leukopenia with neutropenia; thrombocytopenia	Death
31	Gentry and Hill[14]	6½	M	Grand mal Petit mal	?	3 wk.	Anemia; leukopenia with neutropenia	Death
32	Simonsen[15]	8	M	Pyknolepsy	0.9-1.2	4½ mo.	Anemia; leukopenia with neutropenia	Recovery
33	Briggs and Emery[16]	6¾	F	Petit mal	0.6	2 wk.	Leukopenia with neutropenia	Recovery
34	Briggs and Emery[16]	9½	M	Petit mal	...	11 mo.	Anemia; leukopenia with neutropenia; thrombocytopenia	Recovery
12	Van Wezel[11]	54	F	Epigastric aura with choking sensation; unconsciousness	0.9	2 wk.	Dermatitis; anemia; leukopenia	Recovery
35	Michelstein and Weiser[12]	37	F	Petit mal	0.9	2 mo.	Anemia; leukopenia with neutropenia; thrombocytopenia	Death
36	Forster et al.[7]	11	M	Myoclonic	0.9	4 mo.	Anemia; leukopenia with neutropenia; thrombocytopenia	Death
37	Kaplan et al.[7]	21	F	Grand mal	2.1	1 yr.	Anemia; leukopenia with neutropenia; thrombocytopenia	Death
38	Berry[8]	12	F	Petit mal	0.9	9 mo.	Anemia; leukopenia with neutropenia; thrombocytopenia	Death
39	Smith et al.[9]	18	F	Petit mal	2.4	5 mo.	Anemia; leukopenia with neutropenia; thrombocytopenia	Death
40	Klaus[10]	10	F	Petit mal	0.9	1 yr.	Anemia; leukopenia with neutropenia; thrombocytopenia	Death
41	Björn[6]	11	F	Petit mal	0.9	1 mo.	Dermatitis; anemia; leukopenia with neutropenia; thrombocytopenia	Death
42	Grossi-Bianchi and Fistone[5]	14	M	Petit mal	1.5	8 mo.	Anemia; leukopenia with neutropenia; thrombocytopenia	Recovery

authors suggest that the blood picture was the result of a profound hemolytic and granulocytolytic process, with almost complete destruction of platelets. In another patient [56] (Case 13) the bone-marrow findings were consistent with a myelogeneous leukemia or a severe leukemoid reaction, probably the latter.

Lawrence [84] has reported severe hemolytic anemia occurring in a dog given 0.9 gm. of trimethadione a day for one month in treatment of seizures. Curletto and Gasperoni [85] observed depression of all three marrow elements in albino rats given high doses of trimethadione intraperitoneally.

Comment

The clinical usefulness of trimethadione in the treatment of the petit mal triad of absence, akinesis, and myoclonic seizures has been conclusively demonstrated in numerous studies by well-qualified observers. Its clinical usefulness in any other form of epileptic activity has never been clearly demonstrated. My opinion agrees entirely with that of Davis and Lennox [29,31] who feel that it should be used only in the treatment of the petit mal triad and only under medical supervision.

That trimethadione is a potentially dangerous drug is clear from the review of toxic reactions presented. The drug has been implicated in the death of 16 patients whose case reports have been collected from the literature. It is significant that there appears to be no correlation between the incidence of fatalities and the age or sex of the patient, the amount of trimethadione given, or the duration of time during which it has been administered.

Most authors have advocated dosages of between 0.3 and 2.1 gm/day. Since the serious toxicities have occurred in patients on small or moderate doses of the drug, it is clear that these toxic reactions represent sensitivity or idiosyncrasy phenomena rather than overdosage. Therefore, large doses of trimethadione need not be withheld for fear of serious consequences. As illustrated by the three cases presented, the usual doses may be insufficient to control the seizures. Consequently, the use of higher doses of trimethadione may be efficacious in bringing under good control some, and perhaps a significant portion, of those patients with seizures of the petit mal triad who have proved refractory to most attempted therapies and to routine doses of trimethadione. Gibbs [45] is the only investigator found who clearly supports such a view. He states that it may be necessary to raise the dose to high levels (as high as 3.6 gm/day) in some patients and to keep it at such levels in spite of undesirable symptoms of toxicity for a period of time to achieve control. In two of these patients such levels were necessary.

Gibbs notes that once control is achieved at these high levels it will probably be possible to reduce the dosage of trimethadione without recurrence of seizures. This has been possible in two of the patients presented. Several other authors [24,25,27] have also mentioned that it may be possible to reduce the maintenance dosage of trimethadione once control is established. The mechanism underlying this observation is unknown, but it may be related to the gradual increase within the body of the dimethyl breakdown product of trimethadione, which is excreted extremely slowly.

Since the severe reaction of the hematopoietic system is potentially the most dangerous, Davis and Lennox [22,31] have suggested certain precautions in clinical management. They suggest that the drug not be given to patients with a history of blood dyscrasias or pronounced idiosyncrasies to drugs. Although no relationship between such backgrounds and the occurrence of reactions to trimethadione has been shown, this rule is probably a good one to follow for greatest safety.

They suggest further that complete blood studies be performed at monthly intervals to detect possible hematopoietic system responses, that if neutrophils fall below 2500 per cubic millimeter the check be performed more frequently, and that if neu-

trophils fall below 1600 per cubic millimeter the trimethadione be discontinued. This is probably as good a safeguard as can be routinely applied clinically, but its actual usefulness is far from proved. Cases have been reported by Greaves,[71] Briggs and Emery,[49] and Forster and associates[78] (Cases 25, 33, 36) in which such tests were regularly performed and in which the leukopenia and neutropenia progressed to strikingly low levels, even though the drug was stopped. Merlis[80] has gone so far as to state: "There is little to indicate, therefore, that periodic blood counts do much more than provide the physician with a false sense of security." Denhoff and Laufer[87] did very complete studies of toxicity on six patients receiving trimethadione, including bone-marrow examinations. They contrast the lack of information obtained by peripheral blood counts with the sensitivity of changes in the bone marrow. Since marked changes in the bone marrow may occur without any immediate change in the peripheral blood, this may perhaps explain what has frequently appeared to be the catastrophic onset of the severe hematologic manifestations of trimethadione toxicity.

These three cases suggest that the use of high doses of trimethadione may be of value in controlling a group of patients with the petit mal triad who have heretofore proved refractory to therapy. There is no evidence at the present time to suggest that the use of such high doses is of more danger to the patient than the use of the doses ordinarily advocated. It should be pointed out that trimethadione probably should not be employed for the treatment of petit mal seizures until less toxic medications have given inadequate control in maximal tolerated doses. Once there is an indication for the use of trimethadione, however, its application should follow the general rule of anticonvulsant drug management; i. e., the particular medication should be employed in increasing dosage until either satisfactory control or distressing symptoms of toxicity are reached.

Summary

1. Three cases of severe petit mal seizure disorder are reported in which control was obtained only with the use of relatively massive doses of trimethadione (Tridione).
2. The pharmacology, indications for use, recommended dosages, and toxicity of of trimethadione are reviewed.
3. It is concluded that high dosage of trimethadione is of value in controlling certain cases of petit mal epilepsy and that there is no evidence that such dosages are of greater danger from the standpoint of toxicity than are generally accepted dosages.

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Itch Sensation and Recovery of Sensation in Spinal Cord Injuries

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The correlation of itch and other sensations, such as touch and types of pain, has been a matter of controversy for years and has not been settled conclusively.

The purpose of the present work was to correlate the perception of itch in areas of the skin where varied sensory recovery had occurred in spinal cord injuries. This opportunity presented itself on the wards of patients with spinal cord injuries at the Veterans Administration Hospital, Hines, Ill.

Bishop [3] described itch as having the following characteristics: It is elicited from pain rather than from touch areas. It follows as the after-effect of prick, which is itself a mild form of pain. Its effective stimulus is one which persists at one spot rather than requiring movement-like tickle. Itch, like prick or pain, may follow summation of rapidly repeated stimuli, any one of which may be relatively ineffective. Itch does not show adaptation, as does touch. Its central effect is cumulative, like that of pain. This is at least consistent with the inference that itch arises from liminal stimulation of pain endings to a persistingly weak summated state.

Arthur and Shelley [1,2] have isolated the active principle of cowhage and found it to be a proteolytic enzyme called mucunain. The enzyme mucunain is pruritogenic in a dilution of 10^{-1} to 10^{-4} without producing a skin wheal. Increasing the concentration of enzyme injected intradermally never produced pain.

Titchener,[7] in 1909, described well-defined points in skin which, when stimulated with low-intensity current, gave itch sensation and with stronger stimulation caused pain. Graham, Goodell, and Wolff [5] have reviewed this subject intensively.

Bickford,[4] in his experiments relating to itch, found that when the lateral spinothalamic tract was cut, pain and itch were abolished, but not touch. Rothman [6] noted a similar relation of itch to pain and noted itch in the absence of touch but where pain was intact. He also stated that itch was experienced even if epicritic sensation was depressed, as in lesions of the nerve trunk or the central nervous system. Pollock, in discussing this, stated he never found itching in a recovered peripheral nerve lesion.

Zotterman,[8] in 1939, did an electrophysiological investigation of cutaneous sensory nerves, using branches of the cat's saphenous nerve, in respect to itch, pain, and tickling. He produced slight deformities of the hair and skin which produced γ- and C-potentials, often followed by an after-discharge, consisting mainly of C-spikes. Similar findings occurred with rapid pinprick. This he felt provides direct evidence for the view that tickling and itching sensation or reactions are elicited by the activity of thin afferent fibers.

Bishop stated he had been able to produce itch with subthreshold electrical stimuli for pain. The type of current was not detailed.

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Method and Results

In patients who had recovery of pain or touch sensation after a spinal cord injury, careful examination was done and areas were selected in which there was recovery of pain alone or touch alone or other combinations of pain, touch, and temperature. This area and a control area for itch were examined, using itch powder. The patient was not informed as to what to expect but had to tell what he felt, and when. Altogether, 14 patients with quadriplegia and 4 patients with crural paraplegia were examined for the presence of itch sensation. In 27 areas of hypalgesia or decreased to absent sensation to pinprick, where there was good recovery to touch, there was no subjective sensation of itch. In 16 areas where pinprick was felt as exquisitely sharp, itch sensation was felt. In these areas touch was good, and in some cases decreased. In one case pinprick was thought to be good but no itch was felt. Altogether, 44 areas were tested for itch. It can be seen from our results that where pain sensation had recovered to a considerable degree or completely, itching was present. Itching was not correlated with touch sensation.

In order to see whether itch could be produced by low intensities of direct current, we used a constant-current square-wave stimulator and found a sharp pinprick spot on the dorsum of the hand, and the current was then gradually increased.

The first sensation felt was a warm one, then a hot one, then, as the current was increased, a very painful hot sensation. Itch sensation was not felt at all. The current was approximately 20μa. Repetitive stimulation was then tried at a frequency of 1 msec. on, 1-msec. interval; 1 msec. on, 5-msec. interval, and 1 msec. on and 12-msec. interval. With none of these frequencies was itch perceived. Under these circumstances, first a warm tingling sensation was perceived and then a hot burning sensation which was quite painful. Again, the current measured approximately 20μa at either frequency.

In one patient operated upon by Dr. N. Wetzel for pain of vascular origin, bilateral spinothalamic section was done at the fifth thoracic segment. Touch remained intact. Subjective pain still remained, but pain could not be produced by pinprick. He was able to perceive tickle on the thigh but no itch. In six patients with protruded lumbar discs, in whom the sensory findings were very questionable to the decrease of pinprick, itch sensation was absent.

One of the patients used in this study had, in addition to his cord lesion at the sixth thoracic skin segment, a radicular lesion from C-5 to C-8, inclusive, on the right side. This patient had loss of sensation in the right upper extremity to pinprick and temperature sensation but not to touch. Since this injury the patient has had, at times, an allergic urticarial reaction; but, in spite of his hives, he has had no itch sensation in the area where there was a loss of pain and temperature sensation. In the left upper extremity, where sensation was normal, itching was present when the area was stimulated by itching powder. He did not itch on the right, but he did on the left.

Summary and Conclusion

We have examined 14 patients with quadriplegia and 4 patients with crural paraplegia seeking for the presence of itch sensation. There were 44 areas tested for each modality of sensibility. In 27 areas of hypalgesia or decreased pinprick where there was good recovery of touch, there was no subjective sensation of itch when itch powder was used as the stimulus. In 16 areas where pinprick had recovered almost completely, the sensation of itch was felt. In these areas touch was generally conserved, but in some cases was slightly decreased. In one case, despite the recovery of pain, no itch was felt. Itch sensation does not correlate with the presence of touch. The sensation of itching correlates with the preservation of pain.

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Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Wilfred Bloomberg, M.D., President, Presiding

Regular Meeting, March 22, 1956

Upper Thoracic Chordotomy for Relief of Pain: Postmortem Correlation of Spinal Incision with Analgesic Levels in Eighteen Cases.

Dr. James C. White, Dr. Edward P. Richardson Jr., and Dr. William H. Sweet.

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We have been able to examine post mortem the exact position and extent of the chordotomy incision in 18 patients who survived for periods of a week to four years. These lesions are illustrated by photomicrographs and diagrams and are correlated with the clinical level and loss of sensibility to pain.

It is evident that the position of the axons which conduct pain is very variable. The ascending pathways for the perception of pain may occupy the greater portion of white matter in each anterior quadrant. It is unfortunate that the tract is rarely condensed into a compact bundle of fibers between the dentate ligament and the line of emerging ventral rootlets, as illustrated in current neuroanatomical and surgical texts.

While the greater portion of sacral pain fibers tends to lie most posteriorly and laterally, just in front of the dentate ligament and medial to the thin crescent occupied by the ventral spinocerebellar tract, the thoracic fibers lying most ventromedially, and the lumbar fibers in between, we have found that scattered fibers from the buttocks and legs lie well anterior and medial to the motor roots. In rare instances pain in the lumbosacral area has not been relieved by an apparently complete destruction of the contralateral anterior quadrant. A possible explanation for this is that pain-conducting axons may run uncrossed in the ipsilateral spinothalamic tract at least as high as the upper thoracic region.

Degeneration of fibers is often seen far posterior to the dentate ligament in the peripheral portion of the pyramidal tract, at times in the base of the posterior columns, and on three occasions across the median ventral sulcus. This appears to have resulted from contusion of the sensitive white matter by rotation of the cord or compression by the chordotomy hook. In one instance extensive injury to the lateral and dorsal columns appears to have been related to an unusual posterior attachment of the dentate ligaments.

The more extensive transections of white matter have resulted in higher and more consistent levels of analgesia, as well as in much more effective and enduring relief of pain.

Despite these radical incisions, the incidence of disagreeable complications has been infrequent. Only a single patient suffered from persistent leg weakness, and one of nine bilateral chordotomies has led to prolonged difficulty with urination. One unfortunate patient complained of a sense of burning hyperpathia in the area of analgesia. This unusual, but most distressing, complication of chordotomy may have been related to extensive destruction in the posterior portion of the cord.

We conclude that the effectiveness of chordotomy can be increased if the surgeon carries his transverse incision ventral to the dentate ligament to a depth of 5 mm. (nearly to the midline) and cuts across the anterior quadrant to a point at least 2 mm. medial to the emerging line of motor rootlets. This more radical transection involves no added risk of complications provided care is taken not to injure the anterior spinal artery or the posterolateral and posterior columns of white matter.

Discussion

Dr. William H. Sweet: In order to get more information on pain conduction, we have inserted tiny electrodes into the cord with the patient awake. The sensation provoked at low voltage on stimulation in the region of the anterior quadrant, oddly enough, is comparatively mild. It is usually described as some form of sensation of pain or temperature, as one would expect. But if one stimulates electrically the posterior surface of the posterior columns, an intensely disagreeable, usually tingling, sensation is produced. Stimulation within the anterior half of the cord has occasionally evoked ipsilateral pain referred many segments below the level of the electrode so that there was no question about inadvertent stimulus to an entering posterior rootlet. In one patient in whom two chordotomies contralateral to the side of unilateral pain had proved unsuccessful we obtained such ipsilateral responses upon stimulation within the cord and took this as a cue to make an

incision ipsilaterally in the cord. This, happily, yielded relief of the pain. We were thinking of doing an ipsilateral chordotomy on the patient in whom autopsy showed a zone of preserved fibers only 0.5 mm. wide along the anterior median sulcus. In him it seems likely that his unilateral anogenital pain was being transmitted by secondary afferent neurons placed ipsilaterally in the cord, rather than by the contralateral fibers lying in the position of the uncrossed corticospinal motor path.

Dr. James C. White: We learned one thing from Dr. Putnam. When he was severing the pyramidal tract in Parkinsonism, he would insert the knife just lateral to the point of emergence of a posterior rootlet and cut down nearly to the dentate ligament. Despite such an extensive transection of the motor tract, the patient would be hemiplegic for only a week or two. He would soon regain sufficient strength to walk. It is remarkable that you can injure so much of the corticospinal column and not produce more serious weakness of the leg. In our total chordotomy statistics only 4% developed notable leg weakness after a unilateral operation. In the January 1956 number of *Brain*, Nathan and Smith illustrate diagrammatically the extent of transection in a series of postmortem examinations after anterolateral chordotomy. They show a very similar degree of degeneration dorsal to the dentate ligament. They correlated this only with the presence or absence of a Babinski response, not with the degree of weakness in the leg.

Dr. Jerome K. Merlis: I should like to fish for a little information. In the course of some experiments in the cat, I had the opportunity to record from the nucleus ventralis posterolateralis of the thalamus. I noted that both ipsilateral and contralateral pinprick would evoke a response. I have made only a few such observations and do not know whether or not such a response is the rule. Do you know whether this is consistent in the cat, and are there such species differences in the thalamic representation of pain?

Dr. William H. Sweet: A number of investigators have concluded that the pain pathways in the cat's spinal cord are more diffuse than those of man. Of course, one cannot be sure whether the movements a cat makes are indicative of pain. However, Karplus and Kreidl (1925) could not eliminate responses to noxious stimuli applied to the hindlegs of their cats even by complete hemisections on the two sides of the thoracic cord five or more segments apart. The legs appeared to be analgesic only when the hemisections dividing the cord were separated by four or fewer segments. From these observations they concluded that pain impulses in the cat travel in short chains, with much crossing from side to side.

Dr. Jerome K. Merlis: In monkeys?

Dr. William H. Sweet: Mott (1892) divided in monkeys the anterior half of the spinal cord on one or both sides. Postoperatively he could find no evidence of loss of pain sensation. Studies on dogs have been equally misleading as to the effects likely to be seen in man. Cadwalder and Sweet (1912) made careful pre- and postoperative examinations in dogs and found after thoracic anterolateral chordotomy evidence of incomplete loss of cutaneous pain sensibility plus profound ataxia of the hind legs. Histologic analysis revealed operative lesions of the locus an extent which in man usually produce cutaneous analgesia without ataxia.

Dr. D. Denny-Brown: I have two anatomical questions for Dr. Richardson. The root exit zone did not happen to appear in the sections shown. The ventral extent of the lesion seemed to be 2-3 mm. lateral to where I would expect the ventral root to emerge, namely, about opposite the middle of the anterolateral edge of the ventral horn.

My second question is whether pallor in myelin-stained sections accurately represents the extent of the lesion. In experimental lesions of spinal cord in the monkey I have had great difficulty in delineating the exact extent of the lesion if survival has been short. Within the first two weeks there is a zone where myelin stains poorly around the whole line of destruction. The same type of lesion after three months will show a clear-cut edge in myelin stain. In the early stage charting the extent of necrosis with ordinary tissue stains would appear to me to give a more reliable estimate of extent of lesion. It would seem to me that abnormal conduction through partially damaged tracts at the edge of the lesion might give rise to dysesthesias.

Dr. Edward P. Richardson Jr.: It should first be pointed out that the anatomical studies are not yet entirely completed, and that the illustrations shown on this occasion, and the only ones now available, do not necessarily show the full extent of the chordotomy. With respect to the extension of the chordotomy lesion to the anterior root exit zone, it is true that in some cases it did not reach that far anteriorly—even though some of the anterior root fibers emerge more laterally than might be thought. In such cases, pain relief was incomplete, or the level of analgesia was low.

Dr. Denny-Brown is perfectly correct in stating that the zone of pallor in myelin-stained sections does not necessarily represent the true extent of the lesion. We have been able to study the lesions in our material in serial cross sections and have taken the limits of the lesion to be those of the region of total tissue destruction. It is generally not possible to demonstrate the full extent of the zone of totally destroyed fibers in any one section or photograph because the chordotomy incision is generally not absolutely perpendicular to the long

axis of the cord but, rather, somewhat oblique. Extending beyond the limits of the region where fibers are totally severed is one in which some damage has occurred, but it is incomplete; it is this region which shows pallor of myelin staining. Dr. Denny-Brown's suggestion that dysesthesiae might arise from abnormal conduction through such damaged pathways is an interesting one that must be given serious consideration.

DR. WILLIAM H. SWEET: I should like to make another point about the emergence of the anterior rootlets, which has been emphasized by Kahn. These rootlets do not come out along a linear anterior median sulcus. Instead, a cross section of the cord shows some of them passing straight ventrally from the lower medial corner of the anterior horn of gray matter, whereas others come out more and more lateral to this, some passing almost straight laterally from the lower lateral corner of the anterior horn. The site of emergence of an anterior rootlet from the cord is consequently an unsuitable landmark for a precise incision within the cord.

DR. JAMES C. WHITE: We had 20 patients with long survival periods—one to five years. Those people showed no change in vibratory sense, no change in graphesthesia, no change in two-point discrimination. A few of them would feel hairs equally on the analgesic and the normal side. Some might have to have a hair three times as heavy. It seems odd that at least half the cord should be given over to conduction of pain and temperature sensation.

DR. PAUL I. YAKOVLEV: I wish to comment on the organization of central conduction paths in the spinal cord for various modalities of sensory experience. There is a natural tendency to envisage these conduction paths in terms of wiring diagrams. In reality, however, any centripetal sensory excitation once beyond the first synapse may propagate through the entire spinal cord as a universal path to the brain. It is only gradually in the course of phylogeny that the conduction of certain modalities of sensory experience becomes committed to certain anatomically specific long central paths, to the exclusion of other paths. There is a gradient in the differentiation of sensory experience from the universal excitability of all living matter to highly specific (particular) excitability to stimuli such as visual, tactile, and proprioceptive. These latter modalities of sensory experience are committed to central conduction paths, which are anatomically and physiologically highly definitive and correspond almost literally to wiring diagrams of a central telephone board; in the case of visual experience the central conduction path becomes so specific and space committed that it is emancipated from the brain (optic tract) and appears as if it were a peripheral nerve (optic "nerve"). But in the case of pain experience, the most universal modality of experience conceivable, the principle of universality in the organization of central conduction through the spinal cord is largely maintained. The important anatomical fact is that the lateral spinothalamic tract is a polyneuronic system of multiple, overlapping synaptic relays allowing for a wide diffusion of conduction through the spinal cord. In the gamut of experiences which we qualify as pain, there are some modalities of pain experience which are more specific, i. e., less universal than other modalities of pain. Such is the so-called "fast pain" of a pinprick applied to the skin. This relatively specific pain experience is probably conducted through long myelinated fibers of the lateral spinothalamic tract. However, according to all available evidence, even in man there are very few of such long neurons in the lateral spinothalamic tract. The so-called "slow," more universal modality of pain experience, slowly building up from temporal summation of successive subliminal stimuli and outlasting them, is conducted slowly through the huge synaptic surface of multiple relays in the reticulate matrix of the gray matter of the spinal cord and brain stem. The conduction of these modalities of universal pain is not committed to specific long paths. These anatomical and physiological considerations apply to descending systems of conduction as well. The space-committed specificity of conduction from the central cortex to the anterior horns through the corticospinal (pyramidal) tract in primates and man differentiates gradually from a diffuse universal conduction through any available open central paths. In a rat the corticospinal fibers are scattered through the entire cross section of the cord in multiple bundles running through the dorsal, as well as the lateral and ventral, funiculi.

DR. WILLIAM SWEET: In the "analgesic" zone following a chordotomy we have always been able to evoke a disagreeable sensation by stimulation of the skin with bipolar electrodes 2-3 mm. apart carrying a 60-cycle current at 40 to 140 volts. Less frequently, other stimuli may produce pain in the otherwise analgesic zone; examples of stimuli capable at times of eliciting pain in an area analgesic to vigorous single pinprick are (1) compression of an Achilles tendon, (2) testicular compression, (3) pressure against bone (50 lb./sq. in.) (4) hair pulling, and (5) multiple rapid pinpricks.

Medical History of the Ventricular System and Cerebrospinal Fluid. DR. LOUIS BAKAY.

No abstract for this paper is available.

Wilfred Bloomberg, M.D., President, Presiding. Regular Meeting, April 20, 1956

Neuropathological and Neurosurgical Aspects of Postnatal and Natal Cerebral Injuries.

Dr. C. E. Benda and Dr. G. F. Hoessly.

Among the causes of mental disorders of childhood, so-called "cerebral palsies," blindness, and mental deterioration, a considerable role is played by injuries to the brain at the time of birth and early in life.

The case of an 18-month-old infant who fell 30 ft. from a second-story porch to a cement sidewalk and developed unconsciousness, paralysis, and, finally, blindness is presented in detail, with neurosurgical procedures immediately after the accident and clinical and neurological observations over a period of two years and nine months to the time of death, after which a careful neuropathological study was made. The case revealed evidence of the late effects of a concussion of the frontal lobes, and severe encephalomalacia and cystic degeneration of the whole occipital and parts of the parietal lobes in connection with a greatly thickened dura and formation of fluid sacs within the dural sheaths. The mechanism and significance of this pathology are discussed.

Two cases of paranatal injuries and one of a brain trauma a few days after birth, with similar pathology, are presented and a summary given of six cases of cystic degeneration of the brain.

Birth injuries and traumata early in childhood are serious because the lesions interfere with a rapidly growing brain, the development of which is restricted and the immature brain tissue deprived of proper circulation and nutrition, undergoing rather rapid degenerative changes. Among the neuropathological lesions, cystic degeneration of the white matter and encephalomalacia of the gray matter are both most conspicuous. The progressive character of the lesions explains the progressive deterioration and gradual development of blindness observed in several of these cases.

The early diagnosis of brain injuries in infancy and childhood is discussed and a more active neurosurgical approach suggested.

Discussion

Dr. Paul I. Yakovlev: Most of us, I am sure appreciate the always practical slant in Dr. Benda's investigations in the field of pathology of children, in which he is so rightfully eminent. I hope that neurosurgeons will make more authoritative comments than I can do on the issue of indication of extensive surgical intervention in the case of severe head injuries in children. It seems to me that in the case of infants and young children the neurosurgeons would be understandably doubly cautious because whatever happens in the future may be attributed to the operation per se, as well as to the accident of injury. From what Dr. Benda said, it would seem clear, however, that, in view of so much being at stake for the child, the personal risks should be taken beyond what in the circumstances might be considered a reasonable risk. I would like to ask Dr. Benda whether he feels that on the whole infants tolerate and adapt functionally to cerebral injuries and surgical intervention much better than adults. I have seen some remarkable examples of a complete or nearly complete functional recovery, even following what seemed at the time to be a hopelessly crippling damage to the brain.

Dr. Joseph M. Foley: Dr. Benda, what is the evidence that oxygen can produce hyperemia, congestion, and subdural or epidural bleeding? It seems very improbable to me.

Dr. D. Denny-Brown: I want to question that, too. Oxygen does not cause congestion of the brain in the experimental animal. I question whether oxygen after birth, at maturity, has any adverse effect. I would like Dr. Benda to qualify his statement that 24% of cases of mental and spastic defect are related to birth trauma. In such patients in our outpatient clinics, I would think that the figure is much lower. The severe symmetrical damage to the occipital and related cortex in Dr. Benda's case raises the question of damage to the posterior cerebral arteries resulting from herniation by the subdural lesion at the beginning of the illness. The degeneration appeared to me to be consistent with ischemic necrosis.

Dr. Bertram Selverstone: Drs. Benda and Hoessly may be interested to know that we have observed on a number of occasions that the administration of 100% oxygen along with hyperventilation will "shrink" the brain quite considerably at operation. This technique can be very useful when it is necessary to expose a deep structure along the base of the skull. There appears to be considerable vasoconstriction under these circumstances, probably due more to hypocapnia than to hyperoxygenation. The question also arises as to whether there is any reluctance

to perform major neurosurgical procedures at a very early age. Newborn infants tolerate major procedures, both intracranial and spinal, extremely well. The problems which arise in these infants who have had severe intracranial hemorrhages during the process of birth have to do with the fact that bleeding is often multifocal in origin, coming from tears in the bridging veins, the dural sinuses, and the small arteries as well. It would be necessary to perform several craniotomies in order to expose all the sites, in many cases. Most of us feel, therefore, that multiple tapping during the phase of acute bleeding will tend to keep the pressure down while the smaller veins, and perhaps some of the small arterial sources, subside of themselves. Then, if necessary, any major source can be dealt with hours, or even days, later. Perhaps another problem in this community is the separation of obstetrics and neurosurgery, since obstetrics is so often done in specialized hospitals and the patients are not seen by the neurosurgeon as early as Dr. Benda would like. To my mind, the most important problem, however, is one which we really cannot deal with. In my experience, contusion and laceration of the brain are features which are more prominent and of more importance than the hemorrhage and clot formation. I do not think that operative measures can offer much help for this aspect of the problem. These birth injuries have much in common with the so-called acute subdural hematomas seen so often in adults after motor accidents. Actually, these patients are suffering from cerebral contusion and laceration as the major injury, and the subdural hematoma is incidental. The mortality of this lesion is very high, as compared with the extremely benign course of the patient who is operated upon for chronic subdural hematoma.

DR. C. E. BENDA: I am very thankful to the different discussants because the main purpose of this presentation was to stimulate interest of the various branches of medicine dealing with the neuropsychiatric aspects of childhood, and especially with the sequelae of traumata.

As to Dr. Yakovlev's question, I may say that I have had the same experience that some children recover extremely well after a birth injury or injuries later in life, and I am still looking for indications of how we can make an early differentiation of the prognosis. It is also our experience that the immature brain reacts to an injury in a different manner than an adult brain. I am inclined to believe that the glia of the infantile brain is less resistant to external injury and, therefore, seems to be adversely affected, often in the same manner as the brain cells, so that the glia loses its ability to respond to injury and provide reparatory processes. I think that Dr. Spatz proposed such a theory years ago, and I believe that many observations bear out the correctness of his ideas.

As to Dr. Denny-Brown's question about the percentage in our material, I have to refer to several of my publications in which I have tried to analyze our autopsy material. Of course, our autopsy material is "biased," for the reason that it represents a selection of cases that have been institutionalized for reasons of mental deficiency. Moreover, I have always emphasized that the figure of 25% of evidence of vascular circulatory anomalies and injuries refers to the cases of severe mental deficiency, and not to the whole population seen in a neuropsychiatric outpatient clinic. In such a clinic, one sees a great number of different conditions, of which the brain-injured children form only a smaller percentage.

I am sorry that my remarks about the circulatory anomalies under the influence of oxygen were not clear enough, owing to the shortness of available time. I am well aware that oxygen has a vasoconstrictor effect on the arteries and possibly the small veins, therefore causing vasoconstriction and diminished blow flow in those areas. It is, however, also true that if a certain area is hypemic due to vasoconstriction, the blood has to be somewhere else; and that if we have abnormal conditions wtih vasoparesis, as we see so frequently after birth injuries, the blood may be pressed into those areas and oxygen may have a very different effect from what it has under normal conditions. Moreover, there is a great difference between the temporary, short-time use of oxygen and the exposure to oxygen over a period of weeks and months. Although I am not able to provide evidence of the circulatory anomalies caused by the long-term administration of oxygen, it was my intention to suggest that we may find processes similar to those in retrolental fibroplasia going on in the premature brain after long exposure to oxygen.

As to the demyelination which is so conspicuous in the material presented, I did not wish to call it a "demyelinating disease." I wanted to call attention to the occurrence of large areas of demyelination which depended apparently on the injury and which could not have been recognized in etiology except through the study of large hemisphere sections, which provide evidence of the relationship between the demyelinated areas and the periphery.

We have not presented a theory for the details of pathology, because, before forming a theory, it seems important to observe many cases of this type, and only a few have so far been available for study.

Studies on the Mechanism of Copper Deposition in Wilson's Disease. Dr. L. L. Uzman.

Investigations in the past have shown that patients with Wilson's disease are on a continuous positive copper balance (average 0.5 mg/day). That this is due to overabsorption of copper by the intestinal tract also appears conclusively demonstrated. Equilibrium dialysis experiments to determine the avidity for copper binding by tissues were carried out by the author (in collaboration with Drs. F. Iber and T. C. Chalmers). Surgically removed liver tissue from a case of early Wilson's disease was compared with similarly obtained liver tissue from two normal subjects. It could thus be shown that the avidity of the liver for ionic copper was much higher in Wilson's disease. It was also shown by electrophoretic studies that this avidity for abnormal amounts of copper binding could be traced to an electrophoretically distinct fraction among the soluble liver proteins in Wilson's disease. In three other cases of Wilson's disease the author was able to show histochemically a marked difference in the copper content of adjacent lobules. There was a distinct difference in the electrophoretic patterns of lobules with high copper content and those of low copper content. However, those lobules with low copper content still possessed the protein fraction characterized by a high avidity for copper. It is concluded that the avidity for copper resides in a structural abnormality of proteins in Wilson's disease, and that the deposition of copper is secondary to a fundamental defect in protein metabolism.

Discussion

Dr. Allan K. Chalmers: When Dr. Uzman asked me to discuss his paper, I was reluctant to oblige him because I am neither a neurologist nor a biochemist. However, I have been observing from the outside the progress that has been made in the last few years in delineating the pathogenesis of Wilson's disease, and I have been interested in the aspects associated with the liver. As you probably know, there are at least two schools of thought about the relation of copper to the pathogenesis of Wilson's disease. On the one hand, Dr. Uzman has shown you very beautifully tonight some excellent evidence that there is in Wilson's disease a primary defect of protein with a markedly increased affinity for copper. On the other hand, Bearn and Kunkel, and Cartwright and Mahoney believe that the primary defect is one of an inability to manufacture ceruloplasmin, and this deficiency leads to an increased absorption of copper and excessive deposition in the liver and kidneys, with resulting cirrhosis and kidney tubular damage, the latter manifested by amino-aciduria. I was planning to review briefly the data presented by Cartwright, Mahoney, and others as part of my discussion of Dr. Uzman's paper, but I see Dr. Mahoney in the audience, and I am sure he is better able to present his point of view than I.

I should like to ask Dr. Uzman and Dr. Mahoney how they might explain the paradox that in vitro the liver of patients with Wilson's disease has an increased affinity for copper, and in vivo the isotope Cu^{64} disappears from the circulation less rapidly than in normals.

I wish to make one point about the techniques we have seen tonight. At least 5% of patients with Wilson's disease die without ever developing any neurological abnormalities, and a patient recently studied by us had none, not even any changes in her brain at autopsy. It seems possible that many patients with a previous diagnosis of juvenile, or familial juvenile, cirrhosis have had a form of Wilson's disease, and the copper stain demonstrated tonight offers a convenient and simple way of distinguishing these patients from those with simple cirrhosis of the liver.

Dr. Uzman should be congratulated on continuing his significant contributions to the pathogenesis of this fascinating and disheartening disease.

Dr. John P. Mahoney: This paper represents a refreshing new approach to the study of a most interesting disease process. Most of us who have been studying this disease have been impressed by our inability to establish a single concept which would explain all of the biochemical abnormalities. The present work at least represents a new piece of factual information. At the moment I am unable to explain the apparent discrepancy which exists between Dr. Uzman's in vitro observation and our own observations in vivo that radiocopper is cleared from the plasma less quickly in patients than in normal subjects. In addition, normal subjects seemed to localize radioactivity over the liver site after injection of tracer quantities of radiocopper, whereas the patients showed no such localization. The latter observation led us to postulate that the patients' livers were so saturated with copper that they could absorb no more.

I wonder whether Dr. Uzman has studied any other tissues by the techniques demonstrated. The possibility exists that the increased absorption of copper in Wilson's disease is due to some abnormality of the mechanism whereby copper is transported across the intestinal membrane. Demonstration of an abnormal copper-containing protein in the intestinal mucosa might be a clue to the nature of this absorptive defect. In the past it has been suggested that the increased copper absorption was due to the low levels of ceruloplasmin. Our studies demonstrated no correlation between the level of ceruloplasmin and the rate of absorption of copper.

DR. D. DENNY-BROWN: Dr. Uzman's studies have focused attention on the question of protein binding of copper, and in the liver the staining of the liver cells was therefore of great interest. But the same stain applied to the nervous system shows the glia to be stained, not the nerve cells. The Kayser-Fleischer ring is also related to staining of interstitial tissue. Our original idea that Wilson's disease of the nervous system is primarily an alteration of glia appears to be correct. The question therefore arises whether the changes in the liver are related to the excretory function of that organ. The liver is the normal channel for excretion of copper. We found that the bile of patients with Wilson's disease has a normal copper content. The perinuclear structure that begins to stain for copper has the appearance of the Golgi apparatus. As it becomes overstained, the cell becomes degenerate, suggesting a block in the excretory system in the cell and ultimate degeneration of it. This process is not necessarily representative of cellular changes in other organs.

DR. ALFRED POPE: I would like to ask about the nature of the copper complexes presumably formed in the tissues. Does copper form chelate rings with amino acids and peptides, and, if so, what would be the nature of the coordination complexes with the amino acid residues in the peptide chains of the protein? Also, I wonder whether Dr. Uzman would care to speculate concerning the alteration of liver protein structure that might underlie abnormal copper binding capacity.

DR. L. L. UZMAN: I shall endeavor to answer Dr. Chalmers' and Dr. Mahoney's questions together. In talking about the binding of substances by proteins, one has to remember that we are dealing with an equilibrium phenomenon which is determined by a number of factors. In general, the amount of substance X bound by protein Y will be determined by the amount of X still free to bind unless the protein is already fully saturated. Thus ceruloplasmin, which is fully saturated in its copper-binding capacity, will not bind additional copper, but will liberate additional copper if dialyzed under appropriate conditions, so that a copper-free "apo-ceruloplasmin" is obtained. This is not an oxidative enzyme any more, nor is activity restored by adding copper. Presumably, its immunological properties are also lost. Thus, the amount of copper bound by a cell is mainly a function of available binding sites, concentration of free copper ions outside the cell, and the strength with which copper is bound at the available sites. The last factor is especially important in radioactive copper work, where presumably a great portion of the recorded uptake of Cu^{64} by an organ may only represent "exchangeable" copper and not additionally bound copper. This may explain the slow apparent loss of radioactive copper from the plasma of patients with Wilson's disease. Hence it is difficult to reconcile the discrepancies between the actual high affinity for copper of tissues measured directly, as reported there, and results of in vivo work, where none of the factors determining the amount of Cu^{64} bound are known. For example, in a given patient to whom Cu^{64} is administered, we have no idea what his liver copper picture is like. In histochemical procedures, as shown today, would all his lobules appear black, some black and some white, or all white? One thing we do know: All the copper appearing in the urine in this disease has to come from tissue and is not derived from freshly ingested copper, as the work of Matthews and others has shown.

With respect to Dr. Mahoney's second question, I have recently had occasion to study two renal biopsy specimens from patients with Wilson's disease sent by Dr. R. M. Kark, of Chicago. In neither was the copper above normal.

Dr. Denny-Brown's suggestion is a very interesting one, and one to which I have myself subscribed. I believe that the increased copper-binding capacity described for liver is a property of all tissues in this disease; thus also, if a given dose of Cu^{64} is injected, there is no guarantee that it will not be taken up by other tissues first—another point that renders the value of such data doubtful.

What worries me most about the glial changes in the central nervous system, which Dr. Denny-Brown mentioned, is their general significance in terms of the whole disease process. We do know that the disease can manifest itself in families with only liver involvement, and without neurological involvement for many years. Perhaps the stigmatized protein abnormality in different cells and cell systems varies in degree and amount present.

Dr. Pope's question regarding the type of groupings on the liver proteins which are responsible for the increased affinity for copper is a hard one to answer. From the analogy of oligopeptide-copper chelates found in the urine, I am tempted to say that these peptides with copper chelated to them represent fragments of tissue protein breakdown, and that since these peptides have dicarboxylic amino acids as N-terminal residues, the chelation is probably due to a carboxyl-metal ligand. In vitro studies in which competing anions (organic phosphate, sulfate, carboxyl) are offered to remove copper already bound may give a clue as to the type of chelation involved.

I would like to thank all the discussers for the interesting points raised.

NEW YORK ACADEMY OF MEDICINE, SECTION ON NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

Joseph W. Owen, M.D., Chairman, Section on Neurology and Psychiatry, Presiding

Joint Meeting, May 8, 1956

Study of Motives in the "Psychopathic Personality." Dr. James R. Ware and Dr. Kenneth L. Crounse, White Plains, N. Y.

An analysis was made of the case studies of 40 selected patients who had been classified as psychopathic personality with or without psychosis at the New York Hospital, Westchester Division. The material in the hospital records was supplemented by follow-up information. A definite outcome was established in 32 cases. This included 10 social recoveries for a five-year period. In the most successful cases the therapy appeared to have been an amalgamation of active discussion of the psychopathic behavior, confrontation regarding the consequences of actions, and firm admonition. On the basis of associated symptomatology, the 40 patients were found to fall descriptively into three roughly equal groups. The groups each exhibited an internal consistency with regard for (1) certain aspects of the family constellation, (2) the quality of the outcome, and (3) the characteristics of the therapy most effective for that group. The first group represented the classical psychopaths without understandable motivation, and their aberrant behavior yielded only to continual management. The second group revealed a strong schizoid admixture or even a variant of schizophrenic psychosis in the follow-up period. Their families were marked by a wide physical or characterological divergence between the parents. The patients were motivated toward wholly unrealistic goals. The third group were considered to represent a variety of character disorders in which a neurotic acting out had assumed severe proportions. This behavior was seen as an attempt to influence distorted relationships. This group had the best prognosis.

Psychiatric Manifestations in Patients with Systemic Lupus Erythematosus. Dr. John F. O'Connor.

Forty cases of acute disseminated lupus erythematosus seen on the medical service of the Presbyterian Hospital from January, 1950, to September, 1954, were studied. Twenty-one of the cases suffered psychotic episodes. Five had severe neurotic symptomatology. Fourteen were without overt symptoms of a psychiatric nature. The group that was psychotic had a severer form of the disease, evidenced by the length of stay in the hospital and the dosage of cortisone required. Their daily dose was twice the amount required by the nonpsychotic group. Their psychoses became apparent approximately 12 days after the institution of steroid therapy in the hospital, with a maximum of 30 days and a minimum of 2 days. Of the 21 patients who became psychotic, 18 were on steroid therapy at the time. Eleven patients who had psychoses were readmitted and started on equivalent doses of steroids. In only three patients was there a recurrence of the psychosis. There was no evidence of any alteration of symptoms. The reverse seemed to be true, that exacerbations of the medical illness increased the possibility of a psychosis.

Fourteen of the patients had neurological manifestations. These generally, though not always, occurred late in the disease and while the patient was on steroids. The neurological symptoms did not follow any specific pattern, and it was difficult to localize the lesions. Autopsy was done on 11 patients, and 10 had pathologic changes in the central nervous system, particularly the cerebrum. Of the 11, all manifested either psychiatric or neurological symptoms during their lives.

The prognosis for the psychotic episode was good; only one lasted more than three months. Management consisted mainly of psychiatric care and gradual withdrawal of the drug, as indicated medically.

Discussion

Dr. Lawrence C. Kolb: Dr. O'Connor has done us a service in his study on lupus erythematosus, particularly in relation to one point. For some time now it has been the general opinion that patients who have a history of previous psychotic breakdown or emotional disturbance should not be treated with the steroids. This opinion derived largely from the studies of persons who have developed psychotic breaks or other disturbed states in the course of treatment of rheumatoid arthritis. Dr. O'Connor's finding that patients who have had one psychotic breakdown in the course of steroid treatment of lupus erythematosus did not usually become disturbed with the institution of a second course of steroid treatment is therefore a fact of considerable interest. Frequently I have recommended that patients with rheumatoid arthritis who have had a psychotic disturbance in

the past on treatment with steroids should not again be treated. However, the propriety of such a recommendation now is open to question.

Dr. Marvin Stern, Brooklyn: I should like to discuss Dr. O'Connor's paper and compare it with some of the Bellevue material. This is an interesting study and contributes a significant series to a select few large series of patients who have been studied in any one hospital. As the series have been collected, the percentage of psychoses reported has been continually increasing; and this series represents the highest percentage of psychoses I know of, except in the Bellevue series. There is reason for the high incidence in the latter, since the primary reason for patient admission is often psychiatric and these admissions are computed with the general hospital admissions. In terms of the general categories described, the Bellevue material resembles ours except that we see also manic episodes.

In terms of the relationship to cortisone treatment: In all the series now, as the dose and duration of treatment increase, the incidence of psychotic reactions rises. It is important to point out that one cannot with precision correlate statistically the incidence of psychoses with the level of cortisone in a series of patients, or even in the same patient at different times, because those patients who have become psychotic at one level of cortisone therapy return to treatment and are not noted to be psychotic at another level, even higher than the original.

In one-half of our patients who were seriously involved psychiatrically, we felt that the brain damage was related to the lupus activity rather than to the cortisone. Some patients already psychotic received as much as 600 mg. daily for three to four months, with eventual recovery; so one should not be frightened by the psychosis in relation to cortisone. Our feeling is that the psychoses tend to remit, whether with the reduction of cortisone or with the decrease of lupus activity.

I was overwhelmed by the high incidence of brain pathology found at autopsy, and I think this contradicts some of the evidence previously described. We have reviewed the records of closely observed patients who had extensive lupus activity and who had undoubted brain and systemic involvement, and at autopsy we saw only few traces of lupus activity.

Dr. John F. O'Connor: The high incidence of psychoses in the series might be due to the extensive follow-ups we had; and if we could follow all these patients, we might have an even higher incidence. The autopsy correlation was extremely high, and with such a small group may well be coincidental, but pathologic findings in the central nervous system are not uncommon in the literature.

Dr. Richard M. Brickner: Can you tell us more about the neurological picture in these patients during life?

Dr. John F. O'Connor: The neurological picture was out of my field, but, as I said, it was variable. Lesions were difficult to localize. One patient had slight hearing loss. Two of the patients presented themselves initially to a neurologist for examination—one as a quadriplegic. The lupus symptomatology was very much overshadowed by the neurological symptomatology. There was no specific symptomatology, and it was always accompanied on neurological examination by evidence of malfunction in the central nervous system. Interestingly enough, one of the patients presented as a schizophrenic and then manifested symptoms of lupus erythematosus.

Acute Religious Psychotic State. Dr. Lutz Rosenkotter.

A 20-year-old college student, son of a minister, was admitted to New York State Psychiatric Institute after having developed a psychosis of of one week's duration with catatonic and paranoid manifestations and with religious content. This psychosis manifested itself when he had entered a chapel to pray for religious awakening. In doing so, he followed literally the suggestion of his father, with whom he had had arguments of a religious and philosophical nature.

Ministry had been practiced in the father's family for three, and in the mother's family for four, generations, and it was considered a family tradition. The patient's relationship with his mother was marked by lack of warmth and affection; he therefore had identified entirely with his father, at the price of submission under his father's dominance and his rigid religious ideas. He had always identified his father with God; rejection of his father's dogma meant separation from the only source of approval and security, and, at the same time, blasphemy, thus causing unbearable anxiety. When this was pointed out to the patient, he was able to give up his psychotic "retreat from reason" and to work successfully in psychotherapy. He was discharged three months after admission, having received only psychotherapy, and is now continuing his college education without recurrence of psychotic symptoms.

Discussion

Dr. Lawrence C. Kolb: Dr. Rosenkotter's case presentation provides the most manifest account of the occurrence of a religious conversion as the façade for a psychotic reaction. In his adolescent conflict with his father the patient attempted to revolt against the father's authority, which dictated his choice of profession in the ministry. Unable to face his emerging hostility and accept a loss of his dependent relationship on the father,

he selected as a solution the very course suggested by the father prior to his return to college, that is, the conviction of a religious conversion. Here we see that the specificity of choice of symptoms was determined through the parental suggestion; in short, this was the only course of action open to the young man on the basis of his family experiences.

Dr. Rosenkotter is to be congratulated on his able and sensitive management of this particular patient. He provided the initial interpretation which led to the therapeutic opening up of the case and its eventual successful outcome.

DR. GOTTHARD BOOTH: I have been consulting psychiatrist of General Theological Seminary in New York for the past 20 years and have noticed that psychotherapy with people who came from a theological background is generally much easier than it is with the average case. It seems to me that one of the reasons is that people who come from a tradition or an educational background, in the sense that they believe in the reality of the soul more than does the average, more worldly person, are much more responsive to psychotherapy. One can explain it in this way, that in psychotherapy of the average, more worldly person we have to spend most of our time in trying to convince the patient of the reality of the soul, whereas with people who are already convinced and who believe in its reality, the usual time-consuming preparation for therapy has been accomplished beforehand. Over and over again I have seen in my counseling work with theological students, patients I would expect to take a great deal of time for psychotherapy who responded much more quickly than nontheological patients.

DR. LUTZ ROSENKOTTER: I agree with Dr. Booth that this patient responded more readily to psychotherapy because of his spiritual orientation. Religious matters were occasionally discussed in the course of treatment, and I tried to convince the patient that his father's rigid attitudes are not necessarily rooted in Christian religion.

Ruptured Thoracic Intervertebral Disk Causing Cord Compression in a Child. DR. FREEMONT C. PECK JR.

The case was reported of a 12-year-old boy with a calcified nucleus pulposus at T 6 which had ruptured into the spinal canal, causing signs of cord compression. Tomograms of the spine and iophendylate (Pantopaque) myelography clearly defined the lesion. The protruded calcified nucleus was removed at laminectomy, and the cord signs were relieved. A brief review of the pertinent literature and a discussion of the relation between the calcification of intervertebral disks in childhood and peritendinitis calcarae were included.

Heat Studies on Some Neurological Diseases. DR. DEWEY A. NELSON and DR. WILLIAM H. JEFFREYS.

The 84 patients with various diseases of the nervous system included 12 with multiple sclerosis. The patients were first examined as regards vital signs, visual acuity, strength of the extremities, tendon reflexes, plantar responses, dysarthria, nystagmus, range of extraocular movements, pupillary size, and mental state. The patients were then immersed in an ordinary bath tub, to the nippleline, in water of 104 F. The water temperature was then raised to 110 F, and the patients were left in the water for 20 to 30 minutes. During this time they were examined in each category four to five times.

Of the 16 normals, 13 had no neurological change (except mental changes); 2 developed tetany, and 1, a decrease in grip.

Of the 84 patients with neurological disease, 33 had no change except mental changes, and 51 demonstrated alteration in the neurological examination. Seven patients had a decrease in visual acuity. Of these, five had the diagnosis of multiple sclerosis. Four patients showed gross visual field changes, and in two of these the changes were confirmed by immersing the feet and lower legs alone. No patients with multiple sclerosis were examined for visual field changes because of interference of nystagmus. In 33 patients the development of, or increase in, nystagmus was noted. In this group there were 9 patients with multiple sclerosis, 22 patients with diffuse dysfunction of the central nervous system, and only 2 patients with no disease of the central nervous system. Nine patients, all with the diagnosis of multiple sclerosis, developed a medial longitudinal fasciculus syndrome. Six of these patients either had or had developed prior to the onset of the longitudinal fasciculus syndrome more nystagmus in the abducting eye in lateral gaze. Ten patients had reflex changes, all of which involved the ankle jerk only. Sixteen patients with neurological disease showed a change in grip. Four patients had a change in plantar responses—two to normal and two to abnormal. Two patients had seizures; three, ptosis of the lids, and two, individual extraocular muscular palsies; and one patient became unresponsive for a short period.

Vital signs and mental changes observed in this study conformed to those previously described; there were no significant differences in the normal, change, and no-change group.

Individually, the patients in the multiple sclerosis group were most profoundly affected by this experimental situation, but they represented only

25% of the patients who showed neurological changes.

Discussion

DR. RICHARD M. BRICKNER: I should like to ask Dr. Nelson and Dr. Jeffreys if they ever saw any permanent residual effects.

DR. WILLIAM H. JEFFREYS: I am sorry I did not mention that. Most of the changes we saw, and some were quite dramatic, would resolve within 5 to 10 minutes of withdrawing the patients from the hot water. One patient I mentioned who went into coma came out of her unresponsive state in four minutes when we put cold water in the bath. All these changes seem to be rapidly reversible.

DR. RICHARD M. BRICKNER: I ask this question because I have seen some effects which were lasting.

Also, there are experimental situations in which you can offset the neural reactions while the heat (dry) is still on. I have found that vasodilating drugs will sometimes do this in a few cases in which heat impairs visual acuity or induces nystagmus.

Can you make a little clearer what you mean by the statement that multiple sclerosis patients are more profoundly affected than others, and just what you mean by the humoral theory suggestion?

DR. WILLIAM H. JEFFREYS: As to the multiple sclerosis patients being more profoundly affected, this was the only category in which we found more than two neurological changes; many of these patients developed not only the changes which we felt to be those of the medial longitudinal fasciculus syndrome, as you saw in five cases, but visual acuity changes, and also reflex and drift changes. They seemed to have a more widespread manifestation of intolerance to heat.

As far as the humoral theory is concerned, some of these patients developed changes prior to any significant change in vital signs. As you recall, Guthrie was able to reproduce these changes by merely immersing one arm. He was able to get around these changes by putting on an arterial tourniquet. We feel that since these changes are so rapid in onset, and so quickly reversible, and may be produced by immersing a portion of the body, that the most reasonable explanation is the production of some substance in the area that was heated.

DR. THOMAS K. DAVIS: There is only one point I would make in regard to the multiple sclerosis report. One cannot be surprised by what has been reported here. In the treatment of multiple sclerosis there has been a period when many people believed in using fever-producing typhoid vaccine. I do not know whether this is still being done. I never have approved of doing so, and only want to refer briefly to the teaching of Dana, one of this society's really great ancestors. He taught that nothing should be done in the treatment of multiple sclerosis that was strenuous. I do not believe that patients with multiple sclerosis can stand strenuous treatment, or strenuosity in any form.

DR. MORTON NATHANSON: Heat seems to be just one of the conditions that will produce changes in people who have disease of the nervous system. It even may produce measurable neurological changes in the normal subject. It has been shown that heat, severe cold, barbiturates, alcohol, and even high doses of cortisone commonly produce changes in the nervous system. Some of the changes are predictable; others are not. For example, barbiturates may stop certain types of nystagmus, with subsequent improvement in vision. In a given patient it will stop a nystagmus on direct forward gaze and enhance or increase nystagmus on lateral gaze. Then we may observe that a patient with multiple sclerosis who is depressed and under the influence of barbiturates becomes euphoric. I emphasize these points to warn against drawing conclusions as to the etiology of multiple sclerosis based on a change in the conditions of testing.

As to what Dr. Davis said about the use of typhoid vaccine, there were times when high temperatures were said to produce, or to be a contributing factor in producing, a remission in patients with multiple sclerosis. Here was an example in which temperature or heat produced a remission of objective signs.

DR. IRVING J. SANDS: Did you have any EEG's made on these patients?

DR. WILLIAM H. JEFFREYS: No, we did not, because of sweating artifacts.

DR. DEWEY A. NELSON: I should like to emphasize one thing in Dr. Jeffreys' summary and mention one practical point. The first is that neurological changes can be quite transitory. We have seen medical people who have done few neurological examinations seem surprised that they do not see at the bedside today what they were sure they observed yesterday morning. Perhaps neurological changes occur frequently when the patient is febrile, and I think we should all observe for this. For example, Dr. Jeffreys, Dr. Wainerdi, and I, one afternoon at the Hospital for Special Surgery, observed the disappearance of a medial longitudinal fasciculus syndrome on defervescence, with residual dissociated nystagmus, and this occurred over a 90-minute period. This patient had multiple sclerosis.

The second point is that I think we should warn patients with multiple sclerosis against taking unsupervised hot baths, due to the very real danger of their slipping beneath the water.

Transient Displacement of the Pineal Body.

Dr. Bernard Cohen and Dr. Sun Kyoo Song.

The spontaneous return toward the midposition of a previously shifted calcified pineal body was observed in five cases of intracranial disorder. In four cases the displacement was lateral; in one case, posterior. The cause was probably trauma in three cases and vascular disease in the other two. In each case the shift was a significant one, from 4 to 7 mm. Initially, the x-ray findings and the clinical picture suggested the presence of a subdural hematoma or a brain tumor. Despite the pineal shift, all of the patients showed clinical improvement and were treated conservatively. Pneumoencephalography was done in all patients and carotid angiography in two. No surgical procedures were performed. All of the patients had a relatively complete recovery. Edema and/or intracerebral bleeding were assumed to be causing the pineal shift. The conclusion drawn was that even in the presence of obvious pineal displacement the clinical signs must be evaluated carefully. Patients with expanding tumors or subdural hematomas rarely, if ever, show sustained improvement. If this improvement occurs, there is indication for continued conservative management. Thus, patients with edema of the brain or intracerebral bleeding can be spared the placing of unnecessary burr holes, ventriculography, or craniotomy.

Discussion

Dr. Morton Nathanson: I believe it is important to emphasize the management of patients with shift of the pineal body. At one time before the use of angiography, when a patient was admitted to the hospital with a history of head trauma and a shift of the pineal was found, burr holes were made immediately. We found that some of the patients did not have a subdural hematoma, despite the shift of the pineal. However, more recently, angiography is performed where there is a shift of the pineal; and, although there may be bowing of the anterior cerebral artery, there often is no evidence of subdural hematoma. We therefore observe the patient, and, as has been shown tonight, the pineal may shift back to its normal position. More recently in the reported cases of occlusion of the internal carotid artery, it has been not uncommon to find a shift of the pineal. I believe we should bear in mind that a shift in the pineal body per se without any clinical evidence of a downward course should be handled conservatively.

Dr. George H. Hyslop: This is not a discussion; it is a reminder of what the presenter of the last paper perhaps overlooked. He spoke of cerebral hemorrhages as responsible for some of the pineal shift. Cerebral hemorrhages practically all lead to death. We do not have a cerebral hemorrhage produce a transient pineal shift and a relatively benign clinical picture. We are in these cases dealing with a thrombotic reaction and surrounding edema, a long-recognized condition.

Dr. Bernard Cohen: We have seen many patients with vascular accidents, grossly bloody spinal fluid, and localizing cerebral signs in whom there was apparent hemorrhagic involvement of the cerebrum. Many of these patients have later recovered. Since in the cases we presented there was no direct evidence of the pathologic process, we feel that the possibility of extravasation of blood into the substance of one hemisphere must be considered along with cerebral edema as a possible physiological mechanism causing a transient pineal body shift.

SECTION ON
PSYCHIATRY

Anxiety as an Aid in the Prognostication of Impending Death

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The purpose of this paper is to report a series of clinical observations having to do with the prognostication of death in the presence of serious organic disease. These observations are based on the premise that there is an unconscious awareness on the part of the patient of his impending death and that this is reacted to with anxiety which may be repressed. The anxiety, however, is often betrayed by various clinical signs which the alert physician can recognize and use in making a prognosis and planning management.

There are references in the psychiatric and psychoanalytic literature describing unconscious psychologic reactions to organic disease. Freud [1] quotes Aristotle as concluding that "dreams may very well betray to a physician the first signs of some bodily change which has not been observed in waking." He also quotes Hippocrates [1,2] and more recent writers who vouched for the diagnostic value of dreams.[2-5] Jones [6] writes:

> The narcissistic interest in the body, which Freud termed the libidinal complement to egoism, accounts for the interesting occurrence in which bodily disturbances are revealed during sleep long before they manifest themselves in waking life.

Freud elaborates on this narcissistic withdrawal as follows [7]:

> A person suffering organic pain and discomfort relinquishes his interest in the things of the outside world, insofar as they do not concern his suffering. At the same time he withdraws his libidinal interest from his love object. . . The sick man withdraws his libidinal cathexes back upon his own ego. . . . The condition of sleep, like illness, implies a narcissistic withdrawal of the libido away from its attachment back to the subject's own person, or, more precisely, to the single desire for sleep.

In other words, the narcissistic withdrawal during sleep allows for recognition of somatic stimuli from hypercathected diseased organs which were subliminal during waking hours. Under the impetus of maintaining sleep these stimuli are woven into the fabric of a dream.

Ferenczi [8] elaborates further:

> The libido that is withdrawn from the outer world is directed not towards the whole ego, but chiefly to the diseased or injured organ, and evokes symptoms at the injured or diseased area that must be referred to a local increase of libido.

As an example of the diagnostic use of dreams in organic disease Gitelson cites a case of W. Breslin's in which a patient with cancer dreamt that he was in a house in which everything was rotting and falling to pieces. A second patient with an undiagnosed stomach cancer presented a calm façade, but had catastrophic dreams which could be described only vaguely. Necropsy revealed brain metastases. [9]

Eissler [10] relates (page 132) how he diagnosed the recurrence of a breast cancer from a patient's dream, although there were no external evidences. He cites a case of Jones',[11] who diagnosed a cancer of the

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rectum from the psychoanalytic material. Deutsch also reports the accurate prediction of death in a female asthmatic patient from the psychological material.[12] Schilder explains the reactions to impending death on the basis of separation anxiety.[13] An example involving a less severe illness occurred in a dream of one of my own patients which had to do with his waiting in a cafeteria line for pancakes and not being able to get any. On awakening he found himself unable to eat his usual breakfast because of nausea and only later in the day did he develop the severer symptoms of an "intestinal flu."

Further examples of adaptive reactions to physical illness which can be used diagnostically are as follows: Groddeck[14] cites an experience of hysterical anosmia as an effort to escape from an inner awareness of a subclinical recurrence of his own nephritis. The migraine patient who suddenly realizes he has not had an attack for a long time soon learns this is one of his prodromata.[15] The euphorias of patients with multiple sclerosis, tuberculosis, dementia paralytica, and brain tumor are well known and seem to be denial reactions to the inner awareness of physical danger,[9] by way of narcissistic regressions to omnipotent fantasies.[16] Titchener et al., in a study on surgical patients, report that "signs of psychologic disintegration were a sensitive indicator of something going wrong systemically. . . . Early recognition of mental changes may be of crucial importance in alerting the surgeon to growing danger of surgical complication or relapse."[17] A related observation is made by Ellis and Blumberg, who report a higher level of anxiety in patients with fast-growing cancer, in contrast to a lower level of anxiety in patients with slow-growing cancer.[18]

There has been a growing interest in the phenomenon of denial of illness.[19-21] Such denials vary from simple delays in having a physical check-up to reactions which endanger recovery from serious illness.[9] The intensity of the denial varies according to the use made of denial mechanisms in the premorbid personality plus the severity of the organic illness. Eissler comments: "It is remarkable how often patients request medical advice when their complaints are based on psychogenic etiology, and how often they hesitate to go to a physician in the presence of a physical one."[22] Eissler explains these denials on the basis of masochism. But the aspect of significance for this study is that the denial implies an awareness of the illness somewhere in the personality, and that this denial is a manifestation of the return of the repressed.[23] Examples of such denials are seen to an exquisite degree in patients with cancer. In a research project on reactions of cancer patients to their illness, many of us were repeatedly impressed by the appearance of such denials.[24] Uhlman, in relating his experiences with 25,000 cases of nondermatologic cancer, stated he had not seen a single patient who had not denied the nature of his illness.[25] A prototypical example of such patients is furnished by the inmates of hospitals devoted solely to cancer who recognize the cancers of their fellow patients but not their own. Similar observations in patients with severe burns have been reported by Hamburg and associates.[26] This phenomenon is cited as further evidence of an unconscious awareness on the part of a patient of organic disease, plus the intense wish to deny it.

Another phenomenon related to such denials was described by Pfister[27] in a series of observations on survivors of situations in which they suddenly faced seemingly inescapable death. Most of his subjects were Swiss Alpinists.

> He found that the thinking of the person who is certain to die in the next moment goes back to early childhood and refers to situations in which dangers were overcome. It works its way from these activated recollections to the present, ending with a pleasurable, sometimes hallucinatory imagery regarding the future. Since only a few seconds are left to the person, all these processes are sketchy and not more than a few details come to awareness.[10]

So it would seem that in the face of acutely impending death there is a rapid review of past situations of danger which were survived, as though the subject were denying the current reality and reassuring himself that similar emergencies had been survived in the past, plus a further type of reassurance in the form of a hallucinatory wish for the future.

A patient of my own who had capsized in a sailboat far from shore during a sudden storm found himself clinging to the boat and making coital movements, as though to bring on an ejaculation. In analysis it became apparent that among the unconscious attitudes involved was his view of intercourse and ejaculation as potential death. When he thought he was about to drown, he reassured himself that he had survived previous encounters with the mysteries of the deep, and he hoped his present union with the mother-lake would also be survived.

From such examples one becomes aware that there is a potent force within the psyche striving for survival—a "will to live."[28] In the presence of severe organic illness it is manifested as a wish to be well.[20] Bonaparte[29] puts it that "one of man's fundamental wishes is to escape from the insatiable maw of time, the cause of my death."

Another manifestation of this wish to survive occurs in certain types of anxiety dreams, such as before examinations,[30] before trips, or while fateful decisions are pending. The ego reassures itself of previous successes in similar situations of stress. It would seem that one ego mechanism of dealing with new situations of anxiety is to recall previous similar experiences of success.

From a metapsychological point of view the ego institutes a "desperate attempt" to escape a "traumatic situation."[31] This desperate attempt to escape can also be understood as akin to a Zeigarnik[32,33] effect, in which the frustration or failure is projected into the future, producing an increment of motivation to escape the traumatic situation and hence to assure success.

To review, then, the material presented thus far, a somatic illness can sometimes be detected for the first time by its psychiatric manifestations, such as by dreams, by the course of psychotherapy or psychoanalysis, by hysterical symptoms, and by euphoria. There also seems to be a profound need in the psyche to deny the presence of organic illness, especially if it is serious. Related to this denial of organic illness is the phenomenon described by Pfister among survivors of sudden, apparently inescapable, death situations, in which the subjects seemed to reassure themselves by scanning their lives rapidly for previous similar experiences which had been survived and fantasying a pleasant future. These denials seem to be desperate escape measures from a traumatic situation.

During five years as a liaison psychiatrist on the medical wards, there have been several occasions for observing the above-described mechanisms in operation and for using the clinical evidence to make a prognosis of the organic illness and thereby to help the internist in his management of the case.

Report of Cases

Case 1.—A 35-year-old woman was admitted for severe portal cirrhosis with ascites. From the somatic point of view it was apparent she did not have long to live. During a brief routine psychiatric interview she explained that her swollen abdomen was due to a pregnancy. It then developed she had been trying for 15 years to become pregnant, and she held tenaciously to her delusion of final success. This case seemed to fit in with the phenomenon described by Pfister in which the apprehension of death is reacted to with a denial and a compensatory hope for life. Such anosognosia is also reported by Linn.[34]

Case 2.—Another woman, in her late 30's, was admitted for her first hospitalization with malignant hypertension, severe headaches, and insomnia. Blood urea nitrogen was 70 mg. per 100 cc. Physical examination revealed mild retinitis. But on clinical examination one was immediately impressed with her anxious facies, her restlessness in bed, and her plea for understanding as to why she cried so much. She also complained of in-

somnia. Although the physical picture did not warrant it, on the basis of her anxiety reaction and of experience with a previous similar patient, a prognosis of an early demise was made. The patient died within six weeks, of a rapid deterioration of her cardiorenal-vascular system. The prognosis was made on the basis that such severe anxiety manifested the internal awareness of a disintegrative process of such intensity that it could not be attenuated by defensive maneuvers, such as denial or conversion.

Case 3.—A 40-year-old woman was admitted to the medical ward because of severe headaches, nausea, and vomiting. There was a 20-year history of hypertension, and there had been seven pregnancies carried to term. Prior to her hospitalization she had been a patient in the prenatal clinic for a presumed eighth pregnancy, manifested by a cessation of menses, swollen abdomen, and lactation. In her sixth month it was finally established that the condition was a pseudocyesis. Her abdomen deflated overnight, and she awoke with a severe headache, nausea, and vomiting. These symptoms persisted for a month prior to admission.

On the basis of the history of the pseudocyesis plus the long history of hypertension and its recent course, a prediction of early demise was made. On questioning, the patient showed marked anxiety and revealed she had suddenly begun reading the Bible in the previous two months. The patient responded to reassurance, sedation, and antihypertensive drugs for a short time and then began to show signs of clinical deterioration. A decision was made, although not unanimously, to perform a splanchnicectomy. After only one set of splanchnics had been sectioned, the patient went into severe shock on the operating table and died two days later, despite heroic medical efforts. She was conscious for a while the first postoperative day; and when I tried to reassure her, she rejected my hand and shook her head with a gesture of finality that there was no hope.

Although this case was complicated by the surgery, the evidence of the pseudocyesis, the anxiety, and the clinical course seems to support the thesis of an internal awareness of physical deterioration and the consequent elaboration of defensive maneuvers against the anxiety engendered. This appears to be another example of the awareness of impending death turned into an expression of the wish to live.

Case 4.—A woman of 60 with a long history of diabetes, bilateral pyelonephritis, uremia, and hypertension was admitted with a severe cardiac decompensation. Clinically she seemed in extremis; yet she was calm and was able to give herself up to that optimum of passivity which is often essential for somatic recuperation. The lack of anxiety was interpreted as an indication of the relative benignity of her disorder, and the prediction was made that she would live longer than the above cases. She made a rapid recovery from her cardiac decompensation. At the last follow-up she was attending the outpatient clinic, four months later.

There are five similar cases in this series in which the lack of clinical anxiety was used to predict accurately a more benign prognosis in spite of markedly abnormal physical and laboratory findings.

Case 5.—A woman of 40 had been followed on the medical ward for many years, during several admissions for the treatment of sprue. Her disorder consisted of a severe bowel disturbance, blood protein loss, marked edema, and extreme fatigue. Onset occurred shortly after her only pregnancy, during the delivery of which she sustained a massive blood loss and went into shock. During the course of the years and her many admissions I had established a friendly relationship with her; and, although at the beginnings of several of her hospitalizations she seemed in critical physical condition, she would respond to my gestures of reassurance with pleasantries, and she would rally to her medical regimen. But shortly after her last admission, she went into shock, was pulseless, and had no detectable blood pressure. For a short time she seemed dead but finally responded to medical countermeasures. When she was seen the next day, her facies was haggard and drawn, the eyes were deeply sunken, there was a profound expression of terror, and the whole face had a black cast. She looked as though she had been to death's door and would soon return. I tried to resume our friendly relationship, but she immediately rejected me and shook her head with the same hopeless gesture of grim finality as did Patient 3. She, too, died within a few days.

This case illustrates a simple direct expression of the awareness of imminent death.

Case 6.—A man in his late 50's who was experiencing acute anxiety that did not respond to sedation and reassurance was referred for psychiatric evaluation. He had survived two myocardial infarctions five years apart, which occurred on the same calendar day. Since his second episode, some months previously, he had been in cardiac decompensation of varying

degrees. At the time of consultation he was in a moderate degree of decompensation, rested in bed during the day, but was ambulatory and felt better if he could be taken for automobile rides. He was cooperative in interview, but was restless and conveyed the attitude that psychiatric study was pointless. Although a considerable time was devoted to the evaluation, I left him with the feeling I had not learned very much and could not contribute significantly to his management. I awoke the next day from a disturbing dream, mulled over it all morning, and suddenly realized that the patient's anxiety could be due to an awareness of his impending death. His physician was advised of the possibility and was not surprised when, a few days later, the patient developed a severe aggravation of his cardiac decompensation, requiring emergency hospitalization, and died within a week. In retrospect, I thought the begrudging way in which he said "good-bye" to me, plus the clinical setting, served as "day-residue" for my dream.

CASE 7.—A woman of 77 had been treated eight years for bronchiectasis, rheumatoid arthritis, and mild cardiac failure. She had been adjusting realistically to her disabilities and remained active within her capacities. Her illness required occasional hospitalizations, about which the patient complained vigorously, urging her doctor to let her go home—"there is nothing wrong with me." But about two weeks before her last hospitalization there was a marked change of attitude to one of hopelessness and a direct seeking for help. The internist was impressed by the passivity with which she accepted the hospitalization, complaining of not feeling well and of "something wrong." She died suddenly a few days after admission. (This clinical history was furnished by Dr. L. G. Kaplan.)

CASE 8.—One of my psychoanalytic patients reported the diagnosis of a metastatic cancer in his 70-year-old mother. She responded well to her first operation and stoically rejected the use of a cane when a hip metastasis appeared. The hip lesion responded to irradiation. But about six months after the initial diagnosis had been established she became demanding, irritable, and apparently deaf in the presence of all her children except my patient, who was her youngest. Physical studies showed no detectable lesions. Significantly, her physician, who had up to that point been solicitous and competent, lost patience with her, accused her of being neurotic, and told my patient all she needed was "a good bawling out." I surmised that the mother's irritability and peculiar deafness were prodromal to her demise and that her physician's outburst was in response to his knowledge of this and his reactive feelings of helplessness. I advised my patient to be as kind to his mother as possible. Three days later she lost consciousness. Brain metastasis was diagnosed. She died a few days later, and autopsy showed generalized carcinomatosis, with the primary site undetermined. I cite this case as an example not only of an anxiety reaction to unconscious knowledge of disintegration, but also to indicate the possibility that the physician's sudden change in attitude may be used as a diagnostic aid.

Dr. H. M. Serota, in a personal communication, related his experience with an internist in which he used a typical emotional reaction of the latter's to help him accurately to surmise the presence of an undiagnosed cancer in three different cases referred to him for psychiatric evaluation.

Comment

Bernstein[35] has related his experience at a local convalescent home in which over a period of several months three elderly patients announced their own deaths shortly before the event, although physical investigation revealed no apparent change in status to explain their premonitions. With experience one learns to respect such calm announcements. There is usually no difficulty in distinguishing such cases from neurotic fears of death.

The case reports presented above can be distributed as a continuous series demonstrating the manifestations of varying degrees of anxiety to impending death, as

Cases Demonstrating Manifestations of Varying Degrees of Anxiety to Impending Death

Case	Manifestation
5	Simple and direct reaction to horror of death
2	Severe, undisguised anxiety reaction
1	Anxiety converted into a delusion of pregnancy
3	Conversion to a pseudocyesis
8	Hysterical deafness and irritability
6	More subtle manifestations of controlled anxiety and helplessness
7	Direct appeal for help
Cases reported by Bernstein[35]	Calm acceptance of death

shown in the accompanying Table. At one end of the series is Case 5, in which there seemed to be a simple and direct reaction to the horror of death; at the other end are the cases reported by Bernstein,[35] which seem to illustrate the penultimate of a mature acceptance of death. Between are the cases who react with anxiety but have the resources to convert it into various psychiatric symptoms.

The type of reaction to impending death seems to be a function of several factors, such as the acuteness of the organic process, the psychologic maturity of the patient, the extent to which denial mechanisms were used in the premorbid personality, and the attitude of the physician. The absence of clinical anxiety and its derivatives can sometimes be used as an index of the relative benignity of an organic disease despite the presence of markedly abnormal physical and laboratory findings.

The question arises as to why there is a preponderance of uremic and chronic cardiac cases in the series reported. Aside from the fact that such cases are common in general, the fact that a patient has a chronic disease which is susceptible to a sudden change in its equilibrium tends to present a clinical situation in which the patient can more readily become aware of a rapid physical deterioration when it occurs, and react to it with anxiety and denial which can be detected psychiatrically. When such a patient becomes restless and begins to have multiple and insatiable complaints, one becomes alerted to the possibility of an early demise.

What are the practical advantages of suspecting an impending death? There are several. A physician managing a case of severe physical illness may become anxious himself when the patient does not respond to his resourcefulness. His anxiety may be conveyed to the patient, who in turn may react adversely. If the physician is aware of the prognosis and the probable limitations of organic procedures, he can become more supportive in his attitude and furnish the patient with a benign rather than an anxious introject. The patient, knowing he is not alone, garners strength from the physician's kindness, which helps him through this trying and final stage of maturity. Such kindness and care have unconscious significance, which is helpful.[36]

There is, also, the advantage that if the physician is alerted to the likelihood of impending death, he can advise the patient's family appropriately and help more competently in the management of its problems. Kay et al. recently reported the advantages of such prognostications to the efficiency of hospital administration.[37]

Summary

Various ways in which organic disease can be detected from psychiatric and psychoanalytic evidence are reviewed, and case histories are presented in which this knowledge was applied to the diagnosis of impending death. The advantages for clinical management derived from such information are outlined.

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Common Medical Disorders Rarely Found in Psychotic Patients

Rarity of Hay Fever, Asthma, and Rheumatoid Arthritis in Contrast to Relative Frequency of Duodenal Ulcer in a Psychiatric Hospital

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The low incidence of some of the commoner medical disorders in a psychiatric hospital has many practical and theoretical implications. If one has worked, as I have, for several years in an allergy outpatient clinic of a large general hospital, one is especially impressed by the low incidence of allergy of the respiratory tract encountered in psychiatric patients. In spite of the published literature concerning this fact, I have made it my special interest to investigate every sneeze I heard on the wards of the neuropsychiatric VA Hospital, Bedford, Mass., during the fall hay-fever seasons. On practically every occasion it turned out to have been a nurse, secretary, aide, doctor, or other employee, but very seldom a patient. In this paper there will be presented (1) a short review of the literature dealing with the frequency of psychosomatic diseases among psychotics; (2) a report on observations in the VA Hospital, and (3) a discussion of hypotheses which may explain the observed facts.

Review of Literature

Occurrence of Psychosomatic Diseases Among Hospitalized Psychotics.—The general infrequency of psychosomatic illnesses among psychotics has been observed by Swartz and Semrad [1] in their investigation of the occurrence of headaches, hypertension, dermatitis, mucous colitis, asthma, peptic ulcer, and epilepsy among the new admissions during one year in the Boston State Hospital. They found among 587 admissions of psychotic patients in the age group of 16 to 60 years 20 patients who had psychosomatic disorders—an incidence of 3.4%, which they considered very low. They further observed in some patients an alternating occurrence of psychosomatic disorders and psychosis, although in a few patients there was an aggravation of the psychosomatic disorder during the course of the psychosis.

An alternation between psychosomatic illness and psychosis has been noted by several other authors. Appel and Rosen [2] described a case of rheumatoid arthritis which was replaced by a psychosis and one of a psychosis for which was substituted ulcerative colitis. Herman [3] observed the disappearance of migraine during a severe anxiety state; and when this patient's overt anxiety disappeared under psychotherapy, the migraine returned. Kubie [4] reported a patient in whom ulcerative colitis was replaced by severe dermatitis, which, in turn, was replaced by severe migraine. All of these disorders were finally replaced by a psychotic break. Margolin [5] believes that for patients with severe so-called psychosomatic diseases careful psychiatric and psychological examination often discloses an underlying psychotic personality substrate and that such patients frequently alternate between psychological disturbances and their physical disease.

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Occurrence of Respiratory Allergies Among Psychotics.—Quite a number of investigators have studied the occurrence of hay fever and asthma in psychiatric hospitals and have found that the incidence of these diseases there is strikingly lower than in the general population. Estimates of the prevalence of hay fever among the general population vary between 3% (Piness) and 8% (Pipes), and the estimates of the prevalence of asthma in the general population vary between 0.5% (Rackemann) and 3% (Vaughan). Coca and associates,[6] in their textbook, observed that the incidence of asthma, hay fever, and other allergic diseases in the insane is less than 0.1%, as compared with a figure of 3.5% for the population as a whole. Beauchemin[7] and Bernton[8] also reported on the low incidence of hay fever among psychiatric patients. Blaisdell[9] found only two cases of hay fever and one case of asthma among 3700 patients of the Rockland State Hospital (Orangeburg, N. Y.). A similar finding was reported by Reid[10] for 2900 mentally deficient cases of Letchworth Village Hospital (Thiells, N. Y.). MacInnis[11] reported a strikingly low incidence of allergic symptoms in 7000 psychiatric patients. Leavitt[12] found 10 cases of asthma among 11,647 patients with functional psychoses, an incidence rate approximately one-twentieth of the normal rate. In their textbook on allergy, Urbach and Gottlieb[13] discuss the rarity of hay fever and asthma among psychotic patients and remark that "no adequate explanation of these findings has been offered."

In contrast to these opinions, Zeller and Edlin[14] contended that the reported low incidence of hay fever and asthma in psychiatric hospitals is not valid, since psychotics do not complain and therefore their symptoms and signs are overlooked. Zeller and Edlin believed that better medical supervision would reveal that the incidence of hay fever and asthma among psychotics is just as high as in the general population. The authors based their conclusion on finding positive skin tests in 4% of an examined group of patients with various psychoses which they compared with the reported incidence of hay fever in the general population. However, this procedure is open to question, since these investigators did not examine a comparable group of controls (nonpsychotics) by the same procedure. This was done by McAllister and Hecker,[15] who did compare 1875 psychotic patients and 757 hospital employees by means of scratch tests and by examination of the nasal mucous membrane and found an incidence of hay fever of 13% among the employees and 2.9% among the schizophrenics, 1.4% among patients with manic-depressive psychosis, 3% among patients suffering from organic psychoses, but 13% (the same as in the control group) among the epileptics. In summary, then, all papers, with one exception, report a low incidence of hay fever and asthmatic attacks in psychiatric hospitals. There exist, however, some seemingly contradictory observations concerning asthmatic attacks. A great number of writers[2,11,16,24] have seen asthmatic attacks disappear when the patients became psychotic, while others have reported that asthmatic attacks were not influenced,[12] or were even aggravated, by a psychotic state.[2,25] An especially striking example of alternation between asthma and psychosis was reported by Funkenstein.[24]

> A 27-year-old white woman was admitted to the Boston Psychopathic hospital for psychological treatment of severe asthma of many years duration which had not responded satisfactorily to drug therapy. At the time of admission there was no evidence of a psychosis. She failed to improve under psychotherapy. As the asthma was very severe it was decided to try electroshock treatment. Six treatments were given leading to the development of a paranoid psychosis with hallucinations and delusions. This psychosis lasted for four weeks during which time she was free of asthmatic attacks. On recovery from psychosis, severe asthmatic attacks recurred. The patient eventually died in status asthmaticus.

Among the observations on the aggravation of asthma associated with the appearance or aggravation of a psychotic state is a case described by Appel and Rosen.[2] A schizoid personality with paranoid trends is described in which clear-cut paranoid fea-

tures occurred at the same time as asthmatic attacks. Similarly, a patient is described by Hansen [25] whose asthmatic attacks occurred with greater frequency during periods of depression.

Frequency of Gastric and Duodenal Ulcers Among Psychotics.—West and Hecker [26] began their interesting paper with the statement that, despite a general and almost traditional impression that the incidence of peptic ulcer is remarkably low among hospitalized psychotic patients, they could find no evidence in the literature in support of this contention. On the contrary, they cited a number of studies besides their own which showed that the frequency of peptic ulcers found at autopsies on psychotic patients is the same as that in the general population. However, there exist quite different opinions regarding the prevalence of duodenal and gastric ulcer in the general population. Bockus [27] and others believe that about 10% of the general population are ulcer patients. Jennison [28] found chronic, recurring duodenal ulcer in 1.38% of the entire personnel in the home office of the Metropolitan Life Insurance Company, and among the employees over age 30 the frequency of diagnosed cases was 2.4%. Jennison believed that the real prevalence was higher than the rate reported by her, since all employees did not take advantage of the examination in the medical division of the Company. Steigmann [29] reported that of 67,871 admissions to the Cook County Hospital in 1934, a diagnosis of peptic ulcer was made clinically and roentgenologically in 0.88%. West and Hecker,[26] in a total of 3320 hospitalized psychotic male patients, found 33 cases of peptic ulcer, or a prevalence of 1%. They, as well as Pollak and Kreplick,[30] noted that only a small number of psychotic patients reveal clinical symptoms of peptic ulcer. Among the 33 cases of peptic ulcer diagnosed within a four-year period by West and Hecker, only 8 patients complained of epigastric pain and 14 patients offered no subjective symptoms. It is perhaps of even greater significance that, of 18 patients operated on, 16 needed surgery for major complications: 8 for hemorrhage, 5 for perforation, and 3 for obstruction. These complications were, in many of the cases, the first evidence presented of the existence of the lesion. West and Hecker come to the conclusion that the frequency of peptic ulcer in hospital populations of mental and general hospitals is within comparable statistical range and that the reported low incidence is based on increased difficulties of diagnosis in the psychotic patient rather than on actual evidence.

Observations in the Neuropsychiatric VA Hospital, Bedford, Mass.

The experience in the Veterans Administration Hospital can be summarized as follows: It is conservatively estimated that 4500 patients were seen during the last 10 years. Marchand,[31] chief of the medical service of this Hospital, has not discovered a single case of hay fever during this period; there were only 2 cases of bronchial asthma paroxysms and 1 case of active rheumatoid arthritis, but 87 cases of duodenal ulcer and 18 cases of benign gastric ulcer were observed. The accompanying Table shows the prevalence of duodenal ulcers on a certain day (Feb. 21, 1956) and their distribution among the various psychiatric diagnostic groups. The diagnosis of duodenal ulcer in these cases is based on the roentgenologic findings during hospitalization, but may have been established several years ago. No attempt is made in the Table to distinguish between active and nonactive ulcers, or between acute and chronic stages of the psychoses.

The Table shows that in 58 of 1895 patients a duodenal ulcer was found at some time, a prevalence of 3.1% of the whole present hospital population. The prevalence rate among the paranoids was the same as among the whole hospital population. Among 909 nonparanoid schizophrenics there were 19 cases with duodenal ulcer, or an occurrence of 2.1%. The highest prevalence was found among the affective psychoses: Duodenal ulcer had been diagnosed in 11.5%

Male Duodenal Ulcer Cases Among Psychiatric Diagnostic Groups of the Neuropsychiatric VA Hospital, Bedford, Mass., on Feb. 21, 1956

Psychiatric Diagnoses	Number of Patients	No. of Patients Having Duodenal Ulcer	Percentage of Patients Having Duodenal Ulcer
Schizophrenics			
Paranoid	504	16	3.2
Catatonic	345	5	1.4
Hebephrenic	301	8	2.7
Simple	56	1	1.8
Other types	207	5	2.4
Total schizophrenics	1413	35	2.5
Alcoholics	82	5	6.1
Syphilitics	92	4	4.3
Organics	101	6	5.9
Affective disorders	61	7	11.5
Miscellaneous psychotics	51	0	0.0
Total nonschizophrenic psychotics	387	22	5.7
Nonpsychotics	95	1	1.0
Total male patients	1895	58	3.1

of 61 cases. It must, of course, be realized that a roentgenologic examination of the gastrointestinal tract is not performed in every case, but is done only if there is some clinical suspicion of pathology. Since schizophrenic patients diagnosed as catatonic and as hebephrenic are usually more withdrawn than the paranoids and the manic-depressive psychotics, they may never offer complaints. It is conceivable that in the noncommunicative group of patients an ulcer may be more readily missed than among the patients with good communication, and that if all the patients of the hospital were given an x-ray examination some or all of the differences among the various psychiatric groups noted in the Table might disappear. The important point of our findings, however, is that we have seen so many cases of duodenal ulcer and benign stomach ulcer among the patients of our hospital that we are not convinced of the correctness of the opinion that there is a low occurrence of peptic ulcer among psychotics. Rather, we are impressed by the striking contrast between the almost negligible incidence of asthmatic attacks and hay fever symptoms among psychotics and the much higher frequency of duodenal ulcer and gastric ulcer in this group.

Comment

It appears to be of great theoretical, as well as practical, interest to examine which of the existing hypotheses and theories can explain the rarity of hay fever, asthmatic attacks, and acute rheumatoid arthritis in psychotic patients and the (probably) "normal" prevalence of duodenal and gastric ulcers in the same group. Because of the close relationship of these findings to the alternating relationship of some of the psychosomatic diseases and psychoses, hypotheses proposing to explain this alternation will also be included in this discussion. No attempt is made to cite these speculations in historical order, or to give a complete survey of all the published papers. Excluded are all those papers on the psychopathology of asthma, rheumatoid arthritis, and ulcer which have no bearing on the frequency of these disease entities among psychotics. Without deviating from a holistic attitude, we may still divide the papers according to their orientations: (*a*) those with a psychological approach and (*b*) those with a pathophysiological approach.

A. Psychological Theories.—The low incidence of psychosomatic disorders among the psychotic patients led Swartz and Semrad [1] to believe that psychosomatic disorders are in a sense a defense and protection against a psychotic break, and therefore that either a psychosomatic or a psychotic mechanism will prevail. This seemed to be the case in those patients whose psychosomatic disorders disappeared or subsided with the

onset of the psychosis only to reappear in some cases when the psychosis subsided. In these cases, they assumed that the psychosomatic disorder represented a mode of personality or ego functioning which, though defective, was a more mature one than the primitive and infantile ego behavior of the psychotic. Under the duress of certain stresses the more primitive (psychotic) mechanism replaced the relatively more mature (psychosomatic) modes of ego functioning. On the basis of their statistical data, especially the low incidence of psychosomatic disorders among psychotics, they gained the impression that psychosomatic and psychotic disorders tend to be incompatible and that each acts to exclude the other. That Swartz and Semrad's observations are not without exception is demonstrated by the very fact that psychosomatic disorders had been found in some psychotics and by the fact that two of their own cases had psychosomatic symptoms which were aggravated during the psychosis.

A shift from psychosomatic illness to a psychosis is regarded from a psychoanalytical standpoint as a disintegration of the ego to such a degree that the ego could not use the body any more for the expression of the unconscious conflicts. During the psychosomatic illness, on the other hand, the ego has available an organ function for the expression of these conflicts (Deutsch [32-35]).

Sabbath and Luce [36] were especially interested to find in what kind of cases an alternation of asthmatic and psychotic attacks occur and in what cases asthmatic attacks and psychosis may occur together. These writers found in general that those patients who retained their asthmatic symptoms during psychosis showed less break with reality and maintained more nearly intact personalities than those who lost their asthmatic symptoms. Sabbath and Luce are of the opinion that whether a patient retains or loses his asthma attacks appears to be directly related to the extent of his break with reality and, hence, to the depth or level of psychosis.

A conception of Franz Alexander [37] may have a bearing on the special problem of why some of the so-called psychosomatic illnesses are rare, and others, e. g., duodenal ulcer, are not rare, among psychotics. Alexander assumes and emphasizes a fundamental distinction between conversion symptoms and vegetative neurosis.

> A conversion symptom is a symbolic expression of a well-defined emotional content—an attempt at relief. It is expressed by the voluntary neuromuscular or sensory perceptive systems whose original function is to express and relieve emotional tension. A vegetative neurosis like emotional hypertension is not an attempt to express an emotion, but is the physiological accompaniment of constant or periodically recurring emotional states. . . . Asthma has components of a hysterical conversion symptom, since it can serve as the direct expression and partial substitute for a suppressed emotion such as the wish to cry. Breathing—although an automatic function—is also under the control of voluntary innervations. Acid secretion may be a concomitant of an emotional state but is never used for its symbolic expression, as is speech or crying.

Similarly, Deutsch [35] states:

> In situations in which anger, rage or hatred cannot be acted out on the person in question, the breathing movements may take the place of the prohibited action.

In contradistinction to asthma, however, a gastric neurosis consisting of a chronic disturbance of the secretory and motor function of the stomach, is, as Alexander pointed out, not the expression or drainage of an emotional tension but the physiological accompaniment of it. While conversion symptoms take place in the area of voluntary muscles and the sense organs, the vegetative neuroses take place in those parts of the body which are not subject to conscious innervation but are primarily innervated by the autonomic nervous system (Alexander [37]). The difference in the organ systems involved makes it understandable that conversion phenomena manifesting themselves as a paralysis of an extremity, an aphonia, a hysterical convulsion, or even an asthmatic attack, may at times be mistaken to be a purposeful simulation of disease, a kind of malingering. Such suspicion will rarely arise in a true vegetative neurosis. Some reader may question

the validity of subsuming asthma under disturbed function of voluntary muscles, since the outstanding pathophysiological features of an asthmatic attack, namely, the secretion of a glassy, tenacious mucus and the spastic contraction of bronchiolar (smooth) muscles, are both dependent on the autonomic nervous system. One must not forget, however, the important role played by the voluntary musculature in the mode of breathing in general and during an asthmatic attack in particular (Deutsch[35]). Furthermore, the autonomic innervation is not completely independent of the willful innervations, as can be seen in many physiological processes. The acts of swallowing, of urinating, of defecating, and, last but not least, of sexual intercourse are initiated by actions of striated muscles innervated by the cerebrospinal nervous system but accomplished essentially by the autonomic nervous system (Kubie[38]). It is therefore conceivable that in the asthmatic attack a disorganized behavior of the striated respiratory muscles (innervated by the cerebrospinal nervous system) may provoke faulty actions of the smooth bronchiolar muscles and glands (innervated by the autonomic nervous system).

If one accepts Alexander's distinction between conversion symptoms and vegetative neurosis and his theory of their different physiopathology, one may base on this the following hypothesis to explain the contrast in the frequency of the occurrence among psychotics between asthmatic attacks and duodenal and gastric ulcers.

Conversion symptoms are not prone to coexist with a psychosis, because conversion symptoms may actually be able to relieve part of the tension and asthmatic attacks have components of conversion symptoms, according to Alexander.[37] A vegetative neurosis, on the other hand, can coexist with a psychosis, as it does not relieve tensions and is only an accompaniment of emotions, and emotions are undoubtedly present in almost all psychotic states. Only the deteriorated organic psychoses in their end-stages ("vegetable") may perhaps be devoid of emotions. The notion that psychotics live in a world of wish-fulfilling phantasies is probably true for only a very small minority. Many patients are apparently disturbed and afraid, as can be inferred from their behavior: They show signs and expressions of fear and anger. These patients suffer most probably from many of the physiological consequences of such feelings and may, consequently, have disturbances in the secretory and motor functions of their internal organs. This application of Alexander's theory could explain why asthma is extremely rare in psychotics and could also explain why duodenal ulcer is not rare, if a secretory and motor dysfunction of the upper gastrointestinal tract is regarded as one of the factors—probably an important one—in the development of a peptic ulcer. The application of Alexander's hypothesis to our special question encounters two difficulties. (1) It cannot explain the rarity of hay fever and rheumatoid arthritis in psychotics, and (2) gastric juice analyses in psychotic patients have not shown hyperacidity.[39]

Another explanation for the frequent occurrence of duodenal and gastric ulcers in psychotic patients can be hypothesized by assuming that the "peptic" ulcer started in the prepsychotic period, but, as it represents an anatomically changed condition of the gastrointestinal tract and, furthermore, as it often is a self-perpetuating disease, it can still be found in the psychotic state. In this respect, it has to be mentioned that the crippling sequelae of rheumatoid arthritis are sometimes seen in psychotics, though the active disease is rare, and that emphysema of the lungs is sometimes seen, although asthma is rare and emphysema in psychotics may sometimes have been produced by an asthmatic condition in the prepsychotic state (I, however, have not found a history of asthma in those patients with emphysema who were seen on our service). Against this theory, one can present the following facts: Signs of activity of the ulcers are not reported only roentgenologically, but hemorrhages and perforations due to ulcers

are often seen clinically in psychotics and these complications have to be in general regarded as indicating activity of the duodenal or gastric ulcer.

B. Pathophysiological Theories. — There have been various attempts to find a physiological explanation for the observed alternating relationship of asthma and psychosis. Saxl[20] cited the findings of Klemperer[40] and of Tómasson,[41] who found that a shift in the blood electrolytes in psychotic patients occurs and that both an elated and a depressed affect are accompanied by high calcium and low sodium serum values. Saxl hypothesizes that the shift in the ion concentration produced a shift in the vegetative balance such that asthma disappeared in his manic-depressive patient with every severe manic and depressive episode. Funkenstein[24] described a technique of testing the responsiveness of patients to sympathicomimetic (epinephrine [Adrenalin]) and parasympathicomimetic drugs (methacholine [Mecholyl]) and used this technique in psychotics during their psychosis and after recovery. He studied, among many others, six cases with mental illness and a history of asthma and found that the reaction of previously asthmatic patients to methacholine was slight during the psychosis but severe after recovery, at which time also the asthmatic symptoms recurred. That the autonomic nervous system, especially a parasympathetic preponderance, acts as an important trigger mechanism for the provocation of asthma is shown by the precipitation of an asthma attack by parasympathicomimetic drugs, like methacholine, and the termination of an asthmatic attack by sympathicomimetic drugs, like epinephrine.

The Sacklers,[39] in consultation with Ophuijsen, observed that psychotics, in contradistinction to psychoneurotics, tolerate very large quantities of histamine and demonstrated that there was a relationship between histamine tolerance and severity of the psychosis. They connected these findings with the observation of the low incidence of allergies in psychotic patients. The same group of investigators found also a high incidence of achlorhydria and hypochlorhydria in psychotics. Their findings suggested to the Sacklers that an adrenal dysequilibrium exists in schizophrenia. Their investigations along these lines led to the conclusion that adrenocortical activity is increased in psychosis, while, as treatment progresses and clinical improvement becomes manifest, physiological findings point to decreased adrenocortical effects.[39] Similar conclusions can be drawn from Altschule's[42-43] studies on blood eosinophils during the psychosis and after improvement and from Proctor's[44] observation on glucose tolerance curves before and after shock treatment in schizophrenics. It is not appropriate here to summarize and criticize the many, and partly contradictory, statements in the literature concerning the role of the adrenal glands in mental disease. This, however, has been very ably done by Zygmuntowicz[45] in a review article in 1954, and she states in her conclusions:

> Investigations described in the literature indicate a relative over-production of corticosteroids and 17-ketosteroids, possibly the result of prolonged psychologic stress. An excess of these hormones undoubtedly exerts a suppressing effect on the production of the salt-hormone fraction of the adrenal.

The relative preponderance of glucosteroids in mental sickness could simultaneously explain the rarity of hay fever, asthmatic attacks, and active rheumatoid arthritis in the psychotic state and would, at the same time, be consistent with the occurrence of duodenal ulcer. The discontinuance of the preponderance of glucosteroids in patients improving or recovering from the psychosis would be consistent with the recurrence of asthma at that time. Recent research by Zygmuntowicz and Colburn,[46] however, casts doubt on the correctness of the notion that glucosteroids are increased in acute psychotic states. If further research confirms their findings, the above hypothesis for the explanation of the rarity of allergic diseases in psychotics has to be abandoned, or at least very much modified. The psychological and physiological hypotheses discussed are not mutually

exclusive. The physiological explanations may or may not be substantiated by biochemical research.

Summary

Hay fever, asthmatic attacks, and the acute stages of rheumatoid arthritis are extremely rare among psychotic patients.

Duodenal ulcer is not rare in psychotics and is probably just as frequent as in the general population.

An attempt is made to apply existing physiological and psychological hypotheses in the explanation of these facts.

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Brunswik's Theory of Perception

A Note on Its Applicability to Normal and Neurotic Personality Functioning

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About 20 years ago Brunswik[1] published a theory of perception which embodies the concept of probabilistic functionalism. The purpose of the present article is to describe this theory and its application to personality development and functioning, with particular reference to interpersonal transactions.

The term percept is defined in "Webster's New International Dictionary" as "the *meaningful* impression of any object obtained by use of the senses" (italics mine). And it is in this broad sense that the term perception is used in this article, i.e., to include the notion of meaningful awareness of objects. It is of interest here that Allport[2] lists "meaning" as one of the six essential characteristics of the perceptual process and Osgood[3] states that "one would be hard put to draw a defensible distinction between perception and meaning." The latter author accordingly offers the following broad, abstract definition of the term perception as referring "to a set of variables that intervene between sensory stimulation and awareness." In psychological terms, this inclusion of meaning necessarily implies that judgmental, interpretive activity is an integral part of the process of perception. In neurophysiological terms, it implies that the phenomenon goes quite beyond the cortical projection areas of particular sense organs.

According to Tolman and Brunswik, the organism operates in an environment that is a "causal texture in which different events are regularly dependent upon each other. And because of the presence of such causal couplings, actually existing in their environments, organisms come to accept one event as a local representative for another event. . . . The second feature of the environment to which the organism also adjusts is the fact that such causal connections are probably always to some degree equivocal. Types of local representatives are, that is, not connected in simple one-one, univocal fashion, with the types of entities represented. Any one type of local representative is found to be causally connected with differing frequencies with more than one kind of entity represented and vice-versa." Brunswik has emphasized that in the meaningful perception of an object, the organism "is forced to venture an hypothesis"; i. e., it perceives the object "as though" a given cue *a* (or complex of cues) indicates the presence of an entity *b*. Any particular hypothesis of a given *a* as indicating a given type of *b* will have a certain probability of being correct. It is to be noted that the organism's "selection" of a particular hypothesis for perception will depend on its own individual experience with past environments and not on the character of the extant environment. In other words, the veridicality * of the percept will depend

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* A methodological problem is encountered in assessing the veridicality of the percept, i. e., the degree to which the subjective percept conforms to the "actual" object which is perceived. The theoretical difficulty encountered in such an assessment arises from the unique situation of attempting to investigate the accuracy of perception when the investigator must himself make use of perception in carrying out the task. This, it would seem, is theoretically unsurmountable, but for practical purposes it is overcome, or perhaps really bypassed, by the

upon the statistical adequacy or true representativeness of the organism's previous sample of experience.

This probabilistic-functional notion of perception has been incorporated in the "transactional approach" to the study of personality which has been developed by Ames and his associates. No attempt will be made here to review completely the rich body of experimental evidence that has been developed by a number of workers in this field, e. g., Brunswik, Ames,[4] and Ittelson and Kilpatrick.[5] It will be sufficiently illustrative, perhaps, to cite a single experimental result reported by the last two authors. They have demonstrated that when the subject is seated in a darkened room, wears a patch over one eye, and is confronted with two equidistant lights placed in the lower half of the visual field, he will invariably perceive the lower of the two lights as being closer to him. The lower light "looks closer," even though when actually measured it is determined to be the same distance from the percipient as the light located above it. Ittelson and Kilpatrick point out that under ordinary circumstances those objects in the lower extreme of the visual field are closer to the percipient. They suggest then that in this experimental situation it is as though the subject drew upon his countless past experiences in which the lower object was indeed the nearer when he unconsciously assumed and so perceived that the lower light was the closer to him of the two.

These workers and the others cited above have reported on a number of comparable experiments in which the subjects regularly reported unveridical perceptions and in which the departure from veridicality could be understood in terms of the subjects' assumptions or expectations as determined by their past ordinary human experience.

To sum up, then, Brunswik's theory of perception holds that the individual stores up assumption about the world in which he lives and that these assumptions are based upon the principle that cue *a* will be linked with entity *b*, *c*, or *d*, etc., in the current environment with the same frequency as that actually experienced in the past. Thus such an assumption is essentially a probability estimate of the significance of a given cue or complex of cues. Brunswik states further that the subject perceives his world as he thus assumes it to be. Here it may be noted that the "probability estimate" in the process of perception is done quickly and unconsciously. A given individual's aggregate of "assumptions," and hence his particular perceptions of the world, will have much similarity to that of others but will also inevitably be unique to some variable degree.

Thus far, experimental demonstrations such as the one cited above are founded only upon nonveridical instances of perception. As Allport states: "It is not implied that assumptions are not active in veridical perceptions . . . but only that some more positive way of demonstrating them is needed." Further, these experimental demonstrations have been confined to the dimensional and positional aspects of the percept. However, clinical observations, as will be elaborated on below, tend to support the application of this theory to the rich, subtle, nonmeasurable aspects of interpersonal perceptions which have thus far eluded attempts at experimental demonstration. It is hoped, however, that more rigorous, controlled observations that bear on the validation of this theoretical construct, as applied to the area of interpersonal

expediency of accepting "physicalistically" determined data as reliably indicating the "real" characteristics of the object. Thus, the closer the percept conforms to the object as the latter is known by physicalistic means, the more veridical the percept is said to be. For example, if two lines are perceived as parallel, and by actual measurements are shown to be so, the percept is said to be veridical. In the complex matter of interpersonal perceptions, of course, no such simple measuring device is available and the "consensus" of other observers within the same culture has to be relied upon for judging veridicality.

perceptions, can be developed. As mentioned in the preceding footnote, observations in this field will rely upon the "consensus" of percipients other than the subject himself as a device for judging veridicality. In such an employment of "consensus" one actually compares reports of individuals' perceptual experiences rather than the experiences themselves.[8] Therefore, those factors contained in communication, especially language, would necessarily be involved in any consensus.

Let us now consider the implications of the probabilistic-functional theory of perception for an understanding of personality development and functioning. If the experienced subject meaningfully perceives sensory stimuli through association of them with registered past experience, then what of the infant who presumably is incapable of recognizing anything because he has never seen it before? One must assume that at first the infant, in a yet poorly understood way, stores up experiences which come more and more reliably to serve as a basis for his awareness of the interrelatedness of events.

The infant, or child, like the experimental scientist, is involved in accumulating a "series" of experiences or observations. And, as with the scientist, the reliability of his "generalizations" will depend upon the true representativeness of the sample. The organism develops its own set of generalizations or assumptions about the significance of myriads of environmental clues, upon which it comes to rely for its day-to-day impressions of its world. The life span of the individual can be viewed as a continuum, the initial, primarily inductive phase of infancy and childhood gradually giving way to a primarily deductive phase as maturation proceeds.

The likelihood of the individual's sample of experience with particular sensory cues being truly representative of the "universe" is dependent mainly on two factors: the size of the individual's sample or "series" and the heterogeneity of the particular universe. A relatively high degree of homogeneity is characteristic of many inanimate objects and therefore the child is likely, even with a relatively small sample, soon to perceive these objects with a high degree of veridicality; e. g., a small experience with such things as shoes and pencils will suffice for some highly valid generalizations about them. In addition, it so happens that most people come to have a rather rich experience with many such objects. One would expect then, on theoretical grounds, to find that people generally perceive the world of "things" rather veridically, and I know of no clinical evidence that would tend to contradict this.

However, such is not the case when the perceived object happens to be another person. In this special instance, the universe (of human beings) is by contrast vastly more complex and heterogeneous, and, in addition, the child is characteristically exposed in his early (inductive) years to a quite small sample, i. e., his immediate family, as a rule. To the extent to which these few persons happen to be more or less representative of the culture, the child can realistically conceive of and veridically perceive others of that culture. These two factors—the smallness of the sample and the complex variability of the human population (with consequent high equivocality of cues)—lead to the prediction that human beings not uncommonly perceive other persons in individualistic unveridical ways. In fact, it seems likely that in a given human population, the interpersonal preceptions probably range from the relatively veridical in a continuum to the highly unveridical.

It would appear that Brunswik's probabilistic theory of perception leads to conclusions that parallel clinical observations on the problem of psychoneurosis: (1) Both unveridical perceptions and neuroticism are particularly operative in interpersonal transactions; (2) there is no sharp dividing line between those people who tend to operate normally and those who tend to operate neurotically or between those who

tend to perceive veridically and those who tend to perceive unveridically, and (3) experiential determinants play a crucial role in the development of personality and of the faculty of perception.

If the Brunswik view of perception is indeed a valid one, this parallel is not surprising, for it would seem evident that failure of any significant degree in the perceptual process would be of great importance in the matter of adaptation: A person will feel and behave toward others accordingly as he sees them. And, further, again applying Brunswik's theory, a given individual would theoretically tend to misperceive in a rather consistent way from one time to the next, and his particular inappropriate or neurotic behavior would thus tend to be repeated. The well-known patterning of neurotic behavior was labeled the "repetition compulsion" by Freud, who postulated a repressed instinctual drive to explain it. According to the view put forward here, the repetitiveness of neurotic behavior can be at least partially, if not wholly, derived from an enduring mode of unveridical perception. The transference phenomenon deserves special mention at this point.

In the psychoanalytic literature,[6] "transference" has been treated as an essentially emotional phenomenon characterized by the transference of affect from an internal image (e. g., "parental imago") to the therapist; the attitudinal and behavioral consequences of this emotional displacement have received considerable attention. Further, it seems universally agreed that the displaced emotion or affect is at least partially, if not largely, unconscious and repressed. It has received emphasis as something which inevitably occurs in analysis, but, except for some semantic quibbling, most analysts agree that in principle the transference as a psychological phenomenon is ubiquitous in interpersonal relationships. As Hendrick[7] put it: "The phenomenon is a fundamental property of human nature."

However, from the point of view of perception psychology, as described in this paper, one can view the transference phenomenon as simply another instance in which the percipient unconsciously advances on "hypothesis" or a "probability estimate" regarding the significance of sensory cues and perceives the other person, e. g., the analyst or therapist, accordingly. The probability estimate, or assumption phase of the perceptual process, takes place rapidly and unconsciously, although there is no evidence that it is unconscious by reason of repression—just as there is no reason to suppose that the unconscious, assumptive element in perceiving an object, such as a tree, is "repressed." One can further postulate that the subject reacts emotionally to the person as thus perceived and that his own reaction itself has cue significance as it is fed back to him. This is not to deny the well-established significance of emotional attitudes and, indeed, of repressed emotion in the neuroses and in the transference, but it is intended to emphasize that underlying neurotic distortions and inappropriate behavior (such as transference) there is a fundamental perceptual factor operating.

The question arises: What prevents a person who, according to this perception theory, is unveridically perceiving others on the basis of misleading assumptions from acquiring further corrective data about people and so coming to perceive them more veridically? First of all, one might postulate that some unknown physiological factor that hinders new learning develops as a part of maturation and aging. Aside from that, however, there are other hindrances to the acquisition of corrective data that conceptually belong in the realm of psychology. This large and complex subject can be only briefly touched upon here.

Those factors which tend to prevent the person from acquiring data about the interpersonal world which would serve to increase the validity of his "assumptions," and so the veridicality of his perceptions, may be categorized as follows: (1) those that foster "avoidance" and (2) those that foster "pseudoconfirmation."

With regard to the first category, it is apparent that the probability of correctness of the individual's "hypothesis" or "assumption" will increase with the number of cues included; i. e., each new cue that is added reduces equivocality. Therefore when the individual shifts his attention away from the perceived object prematurely or does not take a "second or third look," he avoids the additional cues which, if added, would greatly increase the veridicality of his perception of the particular person. Anxiety, whether of the fleeting, "signal" type or of the full-blown, "felt" variety, can have precisely this effect, and this important consequence of anxiety-determined avoidance, which sabotages opportunities for corrective learning, is seen in the interpersonal isolation characteristic of the schizoid or schizophrenic person. It seems plausible to postulate that in general this avoidance effect operates hand-in-glove with neurotic anxiety.

As mentioned above, there is another broad category of factors which operate to perpetuate the assumptions on which the individual bases his perceptions: those which foster "pseudoconfirmation." For example, an individual may behave toward another in a manner appropriate to his perception of the person and in so doing evoke behavior in the other person which will seem to confirm his original view. There are many clinical examples of such evocative behavior, e. g., the person whose perception of others may lead him to act with trustful friendliness or with hostile suspiciousness and who frequently evokes approximately corresponding attitudes from the person so treated. And these evoked responses, in turn, are noted by the percipient and are treated as data which strengthen his original assumptions. In addition, the emotional responses of the percipient himself may be fed back and, theoretically, be treated as "confirmatory data"; the percipient who views another as fearful, lovable, inspiring, disgusting, etc., may emotionally respond to the percept with fear, love, inspiration, disgust, etc. The emotional response is then itself noted and seems to "confirm" the original assumption about or perception of the object.

Summary

The probabilistic-functional theory of preception as formulated by Brunswik is described.

It is noted that experimental demonstrations of this perception theory have thus far been limited to the dimensional and positional aspects of the percept.

It is proposed that Brunswik's theory of perception has a broad applicability to the study of normal and neurotic personality functioning.

On the basis of the logical application of this theory, it is postulated that an experientially determined, unconsciously assumptive, perceptual component underlies the emotional and attitudinal characteristics of both normal and neurotic behavior. Particular reference is made to the "repetition compulsion" and the transference phenomen. Those factors which tend to perpetuate unveridical perceptions are given brief consideration.

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Studies in the Effects of Lysergic Acid Diethylamide (LSD-25)

Visual Perception of Verticality in Schizophrenic and Normal Adults

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This study is concerned with the effect of change in organismic state, induced by a pharmacological agent, upon spatial localization. Aside from the current concern with the psychological effects induced by the drug, *d*-lysergic acid diethylamide (LSD-25)* the problem has its roots in two lines of investigation: 1. Studies of perception viewed in terms of an organismic theory of behavior, viz., sensory-tonic field theory of perception. 2. Studies of perception from the comparative and developmental point of view; here, the effect of this drug is significant because previous investigations have found that it produces primitive behavior in normal adults.[1,4,6,8]

Sensory-tonic theory of perception, within which the present study was conceived, stands in contrast to traditional theories, which treat perception as a relatively isolated event. According to sensory-tonic theory, perception is held to be not simply a function of stimulus conditions but, rather, a function of the relations obtaining between the impinging stimulus and the ongoing organismic state.[16,17] From this it follows that a change in either the external stimuli or the organismic state will produce a change in perception.

Previous studies carried out within this framework have demonstrated that changes in organismic state can be effectively produced by "extraneous stimulation." By extraneous stimulation is meant stimulation from a source other than the object attended to. To illustrate, auditory stimulation, thermal stimulation, or kinesthetic stimulation through body tilt can be considered "extraneous" if it is present while an observer makes a visual judgment.

Perception of verticality has been shown to be affected by various kinds of extraneous stimulation, e. g., unilateral auditory stimulation, unilateral electrical stimulation of the sternocleidomastoid muscle in the neck, labyrinthian stimulation.[14] It was found that under these conditions the physical position of the apparent vertical (physical position in which a rod is perceived as vertical) shifted to the side opposite the stimulation.[17] Furthermore, when the body was tilted in a chair, with and without support, the subject again adjusted the rod relatively to the side opposite the body tilt.[18]

This paradigmatic situation of verticality has been of particular value in dealing with problems of perceptual development and with psychopathological perception from a comparative developmental point of view. In this connection an ontogenetic study was undertaken to elaborate the changing characteristics of the perceptual behavior

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* Lysergic acid diethylamide (LSD-25) is an ergot derivative, belonging to the ergonovine group. It was first isolated in 1938 by Stoll and Hofmann.[21]

involved in spatial localization as the individual develops. Werner and Wapner, testing 237 children, ages 6-19, for the effects of body tilt on apparent verticality found the following: 1. There is a systematic change in the effect of body tilt on the apparent vertical, depending on the age level: With development, the apparent vertical shifts from a position at the same side as body tilt to a position opposite body tilt. 2. There are developmental changes in the effect of so-called "starting position." By starting position effect is meant the influence that the position of the rod at the beginning of a trial (starting position) has on the final position in which the subject perceives it as vertical: The apparent vertical is displaced from the plumb line in the direction toward the position at which the rod is placed initially. This starting position effect is greatest with the youngest children and decreases with increase in age.[15]

The findings of the study of spatial localization with children have been interpreted within the framework of Werner's developmental theory,[19] which postulates a progressive articulation between self (body) and object. It is in accordance with this view that at early age levels the position of the apparent vertical should be egocentrically tied to the body posture; the developmental shifts of the apparent vertical in the opposite direction reflect a decrease of such egocentricity, or relative independence of external space from changes of body position.†

A number of writers have called attention to the many striking parallels in the structure of the mentality of the schizophrenic and the child.[2,5,9,10] Mental organization in schizophrenia has been described as psychophysically undifferentiated, i. e., in terms of relative fusion of ego and world. The notion of formal similarity in regard to psychophysical undifferentiatedness leads to the hypothesis that there should be an effect of body tilt on apparent verticality in schizophrenics which parallels that found in children. Utilizing this hypothesis, Carini[3] tested two schizophrenic groups—a catatonic-hebephrenic group and a paranoid group—and a normal control group. His findings clearly demonstrated the primitive character of spatial localization in the two pathological groups. Like the youngest children, the catatonic-hebephrenic group adjusted the apparent vertical to the side of body tilt, whereas the normal group adjusted it to the side opposite body tilt. The position of the apparent vertical for the paranoid group fell in between that of the normals and that of the catatonic-hebephrenic group.

In view of (1) the evidence of greater primitivity of perception in schizophrenics and (2) the claim for the primitivizing effect of LSD, we expect the following in regard to the effect of body tilt and starting position on apparent verticality: (1) Under LSD perceptual primitivization would be induced in normals, and (2) in schizophrenics perceptual primitivization would under LSD occur to an even greater extent than already present in these patients. In order to test these expectations, two experiments, one using normals and the other schizophrenics, were conducted.

Experiment 1.
Effect of LSD on Perception of Verticality in Normals

Material and Method.—The subjects for this experiment consisted of 18 normal adults, 11 men and 7 women, ranging from 21 to 38 years of age. The subject, in a darkroom, was seated in a wooden chair with a headrest which prevented head movement. The chair could be tilted manually to the left and to the right. A luminescent rod, the only object visible, was placed 6 ft. from the subject and could be rotated in the frontoparallel plane. The subject's task was to instruct the experimenter to adjust the rod to a position which appeared vertical to the subject.

One-half the subjects were tested first under LSD and then without LSD; the other half were tested in the reverse order; the two sets

† For further elaboration of the theoretical interpretations involved, see Werner and Wapner.[16-17]

TABLE 1.—*Effect of LSD on Perception of Verticality in Normals*

Source of Variation	*df*	F-Tests: Mean Square	*F*	*P*
Between body tilts (B)	2	7,902.99	132.20*	<0.01
Between startline positions (S)	3	720.82	19.04†	<0.01
Between LSD (L)	1	0.28	0.005‡	>0.05
Between subjects (I)	17	42.77	0.63§	>0.05
B×S	6	136.03	8.27‖	<0.01
B×L	2	83.64	5.09‖	<0.01
B×I	34	134.38	8.17‖	<0.01
S×L	3	24.36	1.48§	>0.05
S×I	51	23.68	1.44§	0.05
L×I	17	7.05	0.43§	>0.05
B×S×L	6	9.00	1.56¶	>0.05
B×S×I	102	13.72	2.38¶	<0.01
B×L×I	34	24.59	4.27¶	<0.01
S×L×I	51	5.85	1.02¶	>0.05
B×S×L×I	102	5.76		
Total	431	67.06		

* Tested against pooled error (B×S; B×L; B×I).
† Tested against pooled error (S×I; B×S).
‡ Tested against S×L.
§ Tested against pooled error (B×I; S×I).
‖ Tested against pooled error (B×S×I; B×L×I).
¶ Tested against B×S×L×I.

of conditions were carried out six to nine days apart. Under each of the two major conditions, two further variables were systematically introduced: (1) body position (30 degrees left, erect, 30 degrees right), and (2) starting position of the rod (30 degrees left, 10 degrees left, 10 degrees right, 30 degrees right, of plumb line). There was one trial for each of the 12 combinations of body tilt and starting position. The sequence of the 12 conditions was randomized for each subject; the established sequence was used for the particular subject under LSD and without LSD. The subjects were tested between two and three-fourths and three and one-fourth hours following the administration of the drug or placebo. Sixteen of the subjects received a dose of 40γ (0.04 mg.) of LSD and two subjects received 25γ.

A four-variable (viz., LSD, body tilt, starting position, subjects) analysis of variance design was employed.

Results.—Body Tilt: The *F*-tests are presented in Table 1; Table 2 (upper half) gives the mean positions of apparent vertical under the three conditions of body tilt, both with and without LSD. Irrespective of presence of the drug, when the body is tilted to the left, the apparent vertical is rotated to the right, and vice versa. These shifts increase significantly under drug conditions (body tilt×LSD: $P<0.01$). These effects of drug under body tilt are contrary to our expectation: According to the primitivization hypothesis, it was anticipated that under LSD the apparent vertical would be in a physical position closer to body position; however, rather than coming closer to the side of body tilt, the position of apparent vertical moved even more in the direction opposite body tilt.

Starting Position: The influence of the drug on the starting position effect is shown

TABLE 2.—*Effect of LSD on Perception of Verticality in Normals*
Mean Position of Apparent Vertical (Degrees)*

	Body Position		
	30° Left	Erect	30° Right
No LSD	+7.2°	+0.7°	−6.1°
With LSD	+8.6°	+0.9°	−7.7°

	Starting Position of Rod			
	30° Left	10° Left	10° Right	30° Right
No LSD	−1.9°	−1.1°	+2.8°	+2.5°
With LSD	−2.3°	−1.3°	+2.1°	+3.9°

* A plus sign indicates a position of the apparent vertical clockwise of the plumb line; a minus sign indicates a position counterclockwise.

TABLE 3.—*Effect of LSD on Perception of Verticality in Schizophrenics*

Source of Variation	*df*	F-Tests: Mean Square	*F*	*P*
Between body tilts (B)	2	886.01	4.95*	<0.05
Between starting positions (S)	3	1625.17	19.71†	<0.01
Between LSD (L)	1	112.02	0.67‡	>0.05
Between subjects (I)	17	110.68	0.9[illegible]	>0.05
B×S	6	110.01	4.25§	<0.01
B×L	2	12.86	0.50§	>0.05
B×I	34	191.31	7.40§	<0.01
S×L	3	166.84	6.45§	<0.01
S×I	51	74.23	2.87§	<0.01
L×I	17	21.77	0.84§	>0.05
B×S×L	6	28.72	2.51¶	<0.01
B×S×I	102	18.08	1.58¶	<0.01
B×L×I	34	44.01	3.84¶	<0.01
S×L×I	51	29.02	2.53¶	<0.01
B×S×L×I	102	11.45		
Total	431	61.83		

* Tested against pooled error (B×S; B×I).
† Tested against pooled error (B×S; S×L; S×I).
‡ Tested against S×L.
§ Tested against pooled error (B×I; S×I).
‖ Tested against pooled error (B×S×L; B×S×I; B×L×I; S×L×I).
¶ Tested against B×S×L×I.

in Table 2 (lower half). In keeping with previous experiments, irrespective of presence of LSD, the rod is displaced from the plumb line in a direction toward the position in which it is placed at the beginning of the trial. Under LSD there is a noticeable, though not significant, trend toward increase of this effect (starting position× LSD: $P>0.05$): Without LSD the difference in physical location of apparent vertical under starting position 30 degrees left as compared with 30 degrees right was 4.4 degrees; with the drug, this difference increased to 6.2 degrees. This trend of increased starting position effects under drug is in keeping with expectation (primitivization hypothesis).

Experiment 2.
Effect of LSD on Perception of Verticality in Schizophrenics

Material and Method.—The subjects for this experiment were 18 hospitalized patients, 11 men and 7 women, with a diagnosis of schizophrenia. The distribution of subjects in terms of diagnostic classes was as follows: eight chronic undifferentiated; five paranoid; four acute simple, and one hebephrenic. All subjects were free of any visual defects or physical disabilities. Their mean age was 35 years, with a range of from 23 to 47 years. The median length of time spent in the hospital was three years three months.

The method of procedure was essentially the same as that used for normal subjects in Experiment 1. However, the LSD dose was considerably higher with the patients than with the normals. The rationale for the difference

TABLE 4.—*Effect of LSD on Perception of Verticality in Schizophrenics*
Mean Position of Apparent Vertical (degrees)*

	Body Position		
	30° Left	Erect	30° Right
No LSD	+4.3°	+1.5°	−0.9°
With LSD	+2.7°	+1.1°	−1.9°

	Starting Position of Rod			
	30° Left	10° Left	10° Right	30° Right
No LSD	−0.6°	−0.2°	+2.2°	+5.2°
With LSD	−4.1°	−2.9°	+2.6°	+6.9°

* A plus sign indicates a position of the apparent vertical clockwise of the plumb line; a minus sign indicates a position counterclockwise.

in dose was derived from the observation that schizophrenics have a much higher reaction threshold than normals.‡ Fourteen of the pa-

Results.—Body Tilt: *F*-tests are presented in Table 3; mean positions of apparent vertical with and without LSD are given in Table 4 (upper half). There is no evidence that, for the group as a whole, the drug significantly alters the effect of body tilt on perception of verticality (body tilt×LSD: $P>0.05$).

Starting Position: The changes in effect of starting position on mean position of apparent verticality under LSD are shown in Table 4 (lower half). LSD significantly increases the influence of the starting position of the rod on the final location of apparent vertical (starting position×LSD: $P<0.01$): Without LSD the difference in physical location of apparent vertical under starting position 30 degrees left as compared with 30 degrees right is 5.8 degrees; with the drug this difference increases strikingly to 11.0 degrees. This influence of the drug in terms of an increase in the starting position effect on apparent verticality is concordant with the primitivization hypothesis.

Further Analyses: Comparison of Normals and Schizophrenics in Perception of Verticality Without LSD

In addition to the analyses of the differential effects of LSD reported above, the data from the two experiments may be utilized to inquire into general differences in perception of verticality of normals and schizophrenics. For this purpose, a separate comparison was made of the two groups of subjects with respect to perception of verticality under control conditions, viz., without LSD. A four-variable (viz., diagnostic groups, body tilt, starting position, subjects) analysis of variance design was employed, which for the sake of brevity is not presented here in detail. This comparison should serve as a further test of the primitivization hypothesis, which leads to the expectation of formal similarity in perceptual behavior of schizophrenics and children.

Two comparisons are of interest, one concerning the effect of body tilt and the other concerning the effect of starting position on apparent verticality in normals versus schizophrenics. There are significant differential effects of body tilt, depending on the diagnostic group (diagnostic group× body tilt: $P<0.01$). The mean difference between left and right body tilt for the normals and the schizophrenics can be ascertained from the upper halves of Tables 2 and 4. The mean difference between left and right body tilt is smaller for schizophrenics (5.3 degrees) than for normals (13.3 degrees). Thus, schizophrenics, similar to young children, adjust the rod more in the direction of the side to which the body is tilted than do normal adults.§ These results can therefore be taken as evidence that as compared with normal adults schizophrenics function at a developmentally low level.

On the other hand, the differential effects of starting position for schizophrenics versus normals are not clear-cut. Differential effects of starting position depending on the diagnostic group approaches significance (diagnostic group×body tilt: $P=0.07$). The mean difference in position of apparent vertical between starting position 30 degrees left and 30 degrees right is greater in schizophrenics (5.8 degrees) than in normals (4.4 degrees). Examination of the lower halves of Tables 2 and 4, from which these absolute differences are computed, shows that the effect reflected in the difference scores derives from the right starting position. If normals are compared with schizophrenics for left and the right starting position separately, schizophrenics show

‡ According to data collected by Dr. Harry Freeman, Worcester State Hospital; these data are not yet published.

tients received a dose of 100γ; one received 150γ, and 3 received 200γ. The method of analysis was identical with that employed with normals.

§ See Carini[8] for similar results.

significantly greater effects for starting position right; however, there are no significant differences between groups for starting position left. It appears, therefore, that the expectation derived from a primitivization hypothesis of greater starting position effects in schizophrenics is confirmed only in regard to starting position right.

In summary, the effects of body tilt on perception of verticality in schizophrenics parallel those obtained with children; as to starting position there is only partial evidence supporting such parallelism.

Comment

The results on the effect of LSD may be evaluated in terms of developmental theory. As to the effects of starting position, the various findings are, in general, in keeping with the primitivization hypothesis. Three results are pertinent here: (1) There is a significantly greater effect of starting position under LSD with schizophrenics; (2) similarly, the normals show a tendency for a greater effect of starting position under LSD; (3) moreover, the comparison of schizophrenics and normals under control conditions reveals that there are greater starting position effects in the former as compared with the latter.

For an interpretation of these results on starting position in developmental terms, the critical notion is that of degrees of differentiation between object and self. Lack of differentiation between object and body, indicative of lower developmental organization, is manifested basically in two ways: (1) as a dependency of object on body state (egocentricity), or (2) as a dependency of body status on object stimuli (stimulus boundedness). Extreme starting position effects, for us, represent the latter case; the organism is more or less at the mercy of the changing and lingering effects of stimulus condition; i. e., there are inordinate changes of the organismic state produced by the various stimuli. The consequence of this dependence of the organismic state on the fluctuating stimulus conditions (here the influence of starting position) is a greater lability of perception or interference with stability of framework. Thus, whether we are dealing with an undifferentiatedness due to schizophrenia or due to the changes through LSD, greater starting position effects occur. The experience under LSD of undifferentiatedness of self and object is well illustrated by the report of a normal female subject who showed a very great starting position effect with LSD.

"Both during and after testing it seemed important to associate myself with something real. I felt that I wasn't connected with anything solid and that I was almost floating. There seemed to be no depth or distance, and, in fact, I seemed at times to be disassociated from my body."

Turning now to the effect of body tilt on the perception of verticality, we may first refer to evidence pointing to the changes that are in keeping with a developmental interpretation. The basic evidence comes from ontogenetic studies. There it has been found that for younger children the apparent vertical is located relatively to the same side as body tilt, in contradistinction to the findings for adults, where the apparent vertical is located relatively opposite the side of body tilt. We have already mentioned that this developmental change, for us, reflects a greater egocentricity at early age levels. Piaget exemplifies such a fusion of self and object in the child's spatial organization by pointing to the well-known interpretation made by young children that while walking the moon moves with them.[7] It is in the light of our experimental findings with children that we may interpret, in developmental terms, the differences in spatial organization of schizophrenics and normals without the drug. In the present study, as in Carini's study,[3] for the schizophrenics—as in children—the rod is perceived as vertical when it is in a position more aligned with body tilt than is the case with normal adults.

However, the over-all findings for body tilt under the influence of LSD do not support the primitivization hypothesis as stated: Significant changes in the direction of

greater primitivization under LSD do not occur with schizophrenics; in normals, significant changes do occur under LSD, but, rather than shifting toward perception characteristic of children, the apparent vertical becomes located even more opposite the side of body tilt than without LSD.

Though it is possible that stronger doses of LSD may operate to produce perceptual behavior in normals in keeping with the primitivization hypothesis, it is quite clear that the findings on the effect of drugs as they stand cannot be interpreted in terms of dedifferentiation. Because of the limited evidence provided by this study, much more information is required before one could proceed with a generally acceptable interpretation.

At this time we may just point to an interpretation of this startling result that might give rise to further productive hypotheses. As has been stated elsewhere,[15-17] the location of apparent vertical opposite the side of body tilt is considered, by us, in terms of a counteractive mechanism which compensates for the changes of retinal location of a physically stationary object when the body is tilted: In order to keep the space constant in spite of the variation of body movement, it is necessary to compensate for this variability; without such a counteractive mechanism every displacement of the body would change the world around us. The position of the apparent vertical opposite the body tilt is a reflection of such a compensatory mechanism.

This mechanism works almost perfectly in the light but is exaggerated in the dark. Under ordinary daylight conditions the mechanism is kept within bounds by guiding cues, such as relationships between objects, familiarity of objects, etc.; in the dark such guidance is restricted, and consequently there is an exaggerated operation of this compensatory mechanism manifesting itself in shifts of apparent vertical, not only away from body tilt but even beyond the plumb line. In addition to the external regulators of the mechanism (in terms of objective cues), it may be assumed also that internal controls exist which keep this almost reflex-like mechanism within bounds. It is therefore possible to conjecture that in this situation with adults, where the mechanism has been firmly established, LSD operates to weaken such higher internal controls regulating the compensatory mechanism. The notion that the drug acts as a disinhibitor is supported by clinical observations of the general behavior of the subjects under LSD, such as giggling, inordinate chattering, etc. In this connection we may further mention some recent findings on brain-injured patients; as compared with results for normals, Teuber and Mishkin's data [12] indicate that there is greater displacement of position of apparent vertical opposite body tilt in brain-injured persons, in particular in frontal lobe cases. This, of course, would fit our conjecture on disinhibition, insofar as it is assumed that in such brain-injured patients there is an impairment of the higher controls of the hierarchically organized neural system.

Turning to schizophrenics, one will recall that for this group as a whole no significant changes in effect of body tilt due to LSD were found. This, of course, does not support the primitivization hypothesis, according to which LSD should reinforce the primitive behavior in schizophrenics; i. e., it should decrease the displacement of apparent vertical opposite body tilt. However, if we consider the notion just proposed, that LSD in an adult organism disinhibits the compensatory mechanism, one would arrive at the opposite expectation: Schizophrenics qua adults may exhibit disinhibiting effects under the drug, the effect manifesting itself in an increase in the displacement of apparent vertical opposite body tilt. In the light of these equally possible, but opposite, expectations it is not unreasonable to assume that one type of change operates in some schizophrenics and the other type of change in others. Thus, the lack of influence of the drug in schizophrenics might come about because the effects, opposite for different subjects, may cancel each other out when the total group is considered. Now, return-

ing to the data, if we examine the 18 individual scores, we find that after LSD 9 of the schizophrenics show a decrease and 9 show an increase in displacement of the apparent vertical opposite the side of body tilt. Moreover, a number of subjects in each of these two subgroups show very strong effects. Though these observations are suggestive rather than conclusive, they open the problem whether such differential effects of LSD reliably exist, and, if so, how they are related to differences of pathology within schizophrenia.

Summary

This study is concerned with the effect on spatial localization of lysergic acid diethylamide (LSD), assumed to be a primitivizing drug. Normals and schizophrenics, with and without LSD, adjusted a luminescent rod in a darkroom to apparent verticality under various conditions of body tilt and different initial settings of the rod (starting position).

Without LSD, for normals and schizophrenics, the apparent vertical is displaced in the direction opposite the side of body tilt. Under LSD this displacement is significantly increased for normals; for schizophrenics there is no evidence that the drug significantly alters the effect of body tilt on perception of verticality.

Without LSD, for schizophrenics and normals, the effect of starting position is that of displacement of the apparent vertical from the plumb line in a direction toward the position in which the rod is placed at the beginning of the trial. For normals as well as for schizophrenics LSD increases the starting position effect; this increase is not significant in normals but highly significant in schizophrenics.

The differential effects of LSD are evaluated with reference to the assumption that LSD operates as a primitivizing agent.

Additional comparisons between normals and schizophrenics with respect to the effect of body tilt and starting position on apparent verticality without LSD are included.

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Psychopharmacotherapeutic Research

A Triadistic Approach

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Introduction

Modern psychiatry recognizes three major sources of influence on the psychopathology of the individual patient: the physiologic, the psychologic, and the sociologic. This triadistic approach is not rigorously adhered to by every psychiatrist or by every school of psychiatry, but even the most loyal proponent of the organic, the psychodynamic, or the environmentalist viewpoint usually at least acknowledges the actual or potential importance of one or both of the other two approaches. In clinical practice psychiatrists have for many years utilized a three-pronged attack on mental disease, attempting to alter physiologic influences by, for example, pharmacologic agents, and to change psychologic and sociologic influences by psychotherapy and manipulation of the environment. As knowledge advances in each of these areas, of course, the clinician is in a better position to alter favorably the course of his patient's illness.

We are currently concerned with one aspect of this problem: What is the specific pharmacotherapeutic contribution of certain of the newer agents used in psychiatry? By "specific pharmacotherapeutic contribution" we mean the effect of the drug on the body through physiologic mechanisms. We do not mean the psychologic effects resulting from the fact of our giving something to the patients, with whatever significance that might have to the individual. We further do not mean the group phenomena resulting from the ward reorganization and revitalization which occurs when any experimental program or therapeutic procedure is instituted.

Whenever a drug is prescribed by a doctor for patients in a group, there will be both psychologic and sociologic influences which will act, optimally, as adjuvants to the specific action of the drug. Certainly, we would not wish to eliminate these effects were we able to do so. In research, however, and even in good clinical practice, it is necessary that we be able to estimate their nature and magnitude if we are to determine the actual contribution of a drug to the total therapeutic effort.

Much of our knowledge about the new psychopharmacotherapeutic agents is derived from studies carried out with chronic hospitalized patients. Much of this work has been, perhaps unavoidably, vulnerable to criticisms,[1] owing to the inherent difficulties in dealing with data on several simultaneous planes of analysis. There are, however, distinct advantages to working with chronic patients (e. g., their availability, their cultural stability, their therapeutic resistance and tendency to recidivism, etc.) aside from the obvious fact that we wish to know the effects of drugs on them as a particular group; and if the criticisms could be successfully countered, one would then have a reasonably effective procedure for establishing the merits of available therapeutic agents, distinct from extrapharmacologic factors.

To this end we have initiated an investigation into the effectiveness of four drugs on a chronically hospitalized population. The experiment was so designed as to give information not only as to the effectiveness of each individual drug but also as to the effec-

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tiveness of the various combinations of the agents. The following experimental design was employed in order to ensure that any changes produced in our patients could be attributed neither to unanticipated fluctuations in the course of illness (i. e., "spontaneous improvement") nor to unrecognized modifications in the psychosocial atmosphere, but only, specifically, to the drugs themselves.

Design of the Experiment

A. Establishment of the Base Line

1. *Selection of Patients.* A chronically hospitalized patient population is usually heterogeneous, and it cannot be assumed that any new therapeutic procedure will be uniformly effective against all nosologic entities. This holds true even when the selected subject population is limited to those diagnosed as "schizophrenic," owing to the failure of schizophrenics to respond with any uniformity to therapeutic procedures; for drug-testing purposes they must be considered heterogeneous. Even to specify the number of patients in each subtype is not meaningful unless the differential responses of the subtypes are compared.

For the present investigation the patient population was restricted to female chronic catatonic schizophrenics, matched in respect to age, color, duration of illness, physical health, and uniform bleakness of prognosis. From the 500 female catatonic schizophrenics at Philadelphia State Hospital, 48 white patients, between the ages of 23 and 44, were selected, none with major physical defect or illness, most having previously received the usual somatic treatments. The durations of their illnesses ranged from 6 to 28 years, and the length of hospitalization ranged from 4 to 25 years. The median length of hospitalization was 11 years. The selection did not include the most disturbed patients but, rather, formed a representative group of which some were more disturbed than others. Most patients had received insulin and/or electroconvulsive therapy; some, also pentylenetetrazol (Metrazol), nitrous oxide, and, in some cases, chlorpromazine; the response to treatment had been uniformly unfavorable in the long run.

2. *The Research Unit*

The patients selected were housed in a variety of buildings; it was thus necessary to transfer them to our research ward for an initial period of acclimatization. In theory, it would have been possible to conduct the experiment without transferring any patient. This would, however, have increased the amount of error considerably; additional personnel would have had to be indoctrinated; the data would have been influenced by observers of different orientations and expectations; communication would have suffered, and flexibility in modifying dosages in the face of undesirable side-effects would have been lost. Because of these and other sources of difficulty, it was decided to sacrifice the advantage of keeping the patients in a setting in which an equilibrium had been achieved and substitute the advantages of having a fairly uniform environment for all patients.

The patients were accordingly transferred to a research ward, of which they were the sole occupants. This was an excellent physical facility, with a permanently assigned staff nurse and with two to five attendants on each shift. The most competent attendants available were assigned to the unit. From the standpoint of intensive therapy, more personnel would have been greatly desired; from the research point of view, the personnel represented a satisfactory minimum. Comprehensive laboratory studies were done at the time of transfer, and medical treatment was undertaken by us to correct such conditions as iron deficiencies, urinary infections, and stasis ulcers. Nurses and attendants began to encourage patients to eat adequately and to improve their personal hygiene and appearance. Recreational and occupational therapies were encouraged whenever suitable. Records were kept concerning incontinence, feeding problems, sleep disturbance, and personal cleanliness.

There not being a separate administrator, both administrative and treatment responsibilities resided exclusively with us, who made all decisions jointly. This relationship to the ward made the doctor-patient interaction at the semiweekly ward rounds an inseparable part of the patients' total experience.

3. *Management of Phase I*

For approximately the next seven months the patients did not receive any of the drugs to be tested. Neither did they receive any active chemical, including sedatives, other than antibotics, iron, or vitamins to treat preexisting physical conditions.

It is this fact, and the manner in which this waiting period was utilized, that make this investigation unique, and which is the basis for this communication prior to the report of our findings with the drugs under investigation. We feel that those results will be of interest when they become available, i. e., at the termination of Phase II of the experiment. At this time, however, we wish to call attention exclusively to Phase I, the base line period, because of its implications for the testing of any new drug to be employed.

Whatever the clinical course of these patients would have been, the very fact of their being transferred could be expected to produce a significant change in their clinical condition. How long could this readjustment period be expected to last before a stabilization would occur? To answer this question, some objective measurement of the patients' status at any one time clearly was necessary so that periodic samples could be obtained and compared. We designed rating scales, to be described below, specifically for use with catatonic schizophrenics.

The rating scales, while obviously designed to simplify and objectify the task of clinical observation and recording, nevertheless required us, whose task it was, with the assistance of one of the staff nurses, to do the rating, to gain a good understanding of each patient's mental status, and to obtain through doctor-patient interaction adequate samples of behavior to make the judgments requisite to reliable ratings. It would have been naive to assume that we were mere recording devices and hence had no effect on the patients. It would have been equally naive to assume that we had equal significance for all patients, and that we represented a known environmental influence having no selective effect on the outcome of the experiment. Researchers who fail to deal with this source of bias do not dispose of it by their mere denial of its existence.

Recognizing that we could not be one thing own unavoidable inclinations to help our pato all patients, and in accordance with our tients, we decided to do as much as we could of a psychotherapeutic nature, that is, to attempt to recognize each patient's needs and foster maximum potentiality for growth. Had we not done so, in effect we would have limited artificially each individual patient's opportunity for improvement on our rating scales, and would have served as actual deterrents to those patients whose changing status created in them the greatest need for psychotherapy. Naturally, our own transference reactions helped determine which of the patients received the greater part of our attention. This inequity might seem to offer a potential source of error; but when the manner of formation of our subgroups is described, it will be seen that controls for this type of error are "built into" the experimental design.

Rounds were made twice a week in the day room, lasting one to two hours. The patients were seen there individually and in small spontaneous groups as these developed. Ratings were made on the clinical status of each patient in the initial week on the unit and at 12 and 28 weeks.

4. *The Rating Scales*

There have been many attempts to supplement or sharpen clinical impressions of patient status or improvement by rating scales, check lists, etc. None of the methods was suitable for our particular needs, i. e., for an instrument with a range extending from severe regression through normality, simple in design, and relatively immune to subjective bias. In the catatonic, and in other clinical groups, the psychopathology, involving thinking, feeling, and acting, is reflected in the composite of motor behavior, verbal behavior, and social behavior. In each of these components behavior may deviate from the normal in the direction of either excess or insufficiency. For example, catatonic excitement or stupor are equally deviant from normal motor behavior in that the one represents the extreme of hyperactivity and the other that of hypoactivity. Utilizing such behavioral terms makes possible the employment of still another dimension, that of time, as a means of expressing degree of deviation. Thus, a patient may be inappropriately overtalkative most of the time (more than 50%), or he may be predominantly hypotalkative. If social behavior is depicted in both its general and its specific aspects, it is possible to characterize, for example, the patient who has the ability to get along superficially with many people, but cannot form friendships; or his opposite may be equally well characterized. Here, too, time can be used as a measure of the stability and adequacy of this capacity. For simplicity, six scales—Greater Motor Behavior, Lesser Motor Behavior, Quantitative Verbal, Qualitative Verbal, General Interpersonal Relationships, and Specific Interpersonal Relationships—were set up, each with a possible deviation of +3 or −3, zero representing the norm.

TABLE 1.—*The Rating Scales*

Greater Motor Behavior: Gross bodily activity	
+3	Constantly hyperactive
+2	Usually hyperactive
+1	Occasionally hyperactive
0	Normally active
−1	Occasionally hypoactive
−2	Usually hypoactive
−3	Constantly hypoactive
Lesser Motor Behavior: Finer manipulative movements	
+3	Continual nonproductive movements
+2	Usually hyperactive
+1	Occasionally hyperactive
0	Normal
−1	Occasionally hypoactive
−2	Usually hypoactive
−3	Constant hypoactivity
Quantitative Verbal Behavior	
+3	Constantly hypertalkative
+2	Usually hypertalkative
+1	Occasionally hypertalkative
0	Normally talkative
−1	Occasionally hypotalkative
−2	Usually hypotalkative
−3	Constantly hypotalkative
Qualitative Verbal Behavior: Speech as communication	
+3	Conventional speech but always noncommunicative
+2	Conventional speech but usually noncommunicative
+1	Conventional speech but occasionally noncommunicative
0	Normal speech
−1	Occasionally bizarre
−2	Usually bizarre
−3	Always bizarre
General Interpersonal Approach-Avoidance Behavior	
+3	Constant undiscriminating approach behavior
+2	Predominant undiscriminating approach behavior
+1	Occasional undiscriminating approach behavior
0	Normal relationships with people in general
−1	Occasional undiscriminating avoidance behavior
−2	Predominant undiscriminating avoidance behavior
−3	Constant undiscriminating avoidance behavior
Specific Interpersonal Approach-Avoidance Behavior	
+3	Invariable strong emotional display to at least one specific person
+2	Usual strong emotional display to at least one specific person
+1	Occasional strong emotional display to at least one specific person
0	Normal relationships with at least one specific person
−1	Occasionally avoids at least one specific person
−2	Usually avoids at least one specific person
−3	Invariably avoids at least one specific person

Each of these behavioral characteristics may be gauged quantitatively according to the proportion of waking time through which it is manifested. Thus, a 3-point deviation signifies relative constancy; 2 points, the predominant or usual (more than 50% of the time) mode; 1 point, occasional deviation, and 0, what would be appropriate behavior in these particular circumstances, i. e., within the limited possibilities for expression offered on the unit.

From Table 1 it may be seen that a patient may have a maximum deviation of 3 points (sign being disregarded) on each scale, with a total possible maximum deviation of 18 points. As a patient improved, his total number of deviations would decrease toward zero.

Results of the Waiting Period

The median score for our experimental population at the time of initial evaluation (during the first week) was 16, with a range of 8 to 17. The patients were rated twice more during Phase I, the base line period, at 12 and at 28 weeks. Table 2 shows the rating of each patient, both in terms of total deviation scores (Columns 2 and 4) and in terms of change since the preceding rating (Columns 3 and 5). Column 6 shows the net change during Phase I, obtained by algebraic summation of Columns 3 and 5. The range was from −11 (improved) to +4 (worse), with a median at −2 and a mean of −2.4. The Figure, in the form of a scatter diagram, shows the relationship between net change and initial rating. It is evident that no striking correlation exists between these two variables, and it is accordingly safe to say that improvement during Phase I was not a function, either direct or inverse, of severity of symptoms as measured by our rating scales.

TABLE 2.—*Patients' Initial Ratings and Change Scores During Phase I*

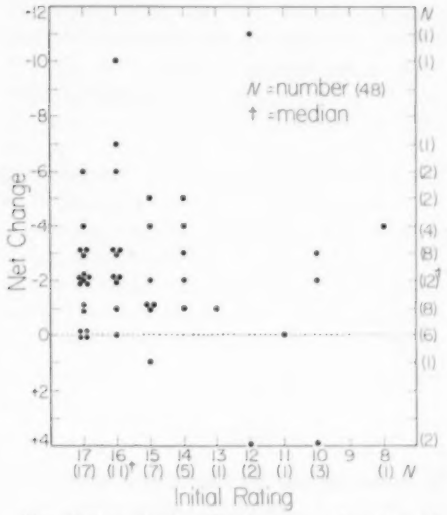
Patient	(1) Initial Rating Total	(2) 12 Weeks Total	(3) 12 Weeks Change	(4) 28 Weeks Total	(5) 28 Weeks Change	(6) Net Change
1	15	14	−1	11	−3	−4
2	11	11	0	11	0	0
3	14	11	−3	12	+1	−2
4	15	11	−4	10	−1	−5
5	14	12	−2	9	−3	−5
6	17	15	−2	15	0	−2
7	17	17	0	17	0	0
8	16	13	−3	13	0	−3
9	12	4	−8	1	−3	−11
10	12	17	+5	16	−1	+4
11	17	14	−3	16	+2	−1
12	15	14	−1	13	−1	−2
13	10	10	0	8	−2	−2
14	17	16	−1	14	−2	−3
15	17	16	−1	15	−1	−2
16	16	14	−2	6	−8	−10
17	16	12	−4	13	+1	−3
18	8	6	−2	4	−2	−4
19	10	9	−1	7	−2	−3
20	17	17	0	17	0	0
21	16	12	−4	9	−3	−7
22	17	17	0	17	0	0
23	14	12	−2	10	−2	−4
24	10	11	+1	14	+3	+4
25	13	14	+1	12	−2	−1
26	16	14	−2	14	0	−2
27	17	17	0	15	−2	−2
28	17	17	0	16	−1	−1
29	16	16	0	16	0	0
30	15	14	−1	14	0	−1
31	16	15	−1	14	−1	−2
32	14	11	−3	11	0	−3
33	16	16	0	10	−6	−6
34	16	10	−6	13	+3	−3
35	15	16	+1	16	0	+1
36	17	16	−1	14	−2	−3
37	17	17	0	17	0	0
38	16	15	−1	15	0	−1
39	15	16	+1	14	−2	−1
40	17	16	−1	14	−2	−3
41	17	16	−1	13	−3	−4
42	15	13	−2	14	+1	−1
43	16	15	−1	14	−1	−2
44	17	17	0	15	−2	−2
45	17	12	−5	11	−1	−6
46	14	14	0	13	−1	−1
47	17	16	−1	15	−1	−2
48	17	14	−3	15	+1	−2
Medians	16	14	−1	13	−1	−2

The important information to be derived from Phase I is that, as a result of various influences during the waiting period, 39 of our 48 patients showed measurable improvement (which was striking in several cases), 6 remained unchanged, and 3 were worse. This result was accomplished without drugs, intensive individual psychotherapy, or "total push."

From a nursing standpoint, the patients were considered in terms of six types of problems not covered by the rating scales: sleeping, eating, incontinence for urine, incontinence for feces, retention of feces, and personal cleanliness. Table 3 indicates the number of patients presenting problems of this sort during each of the three rating periods.

It is apparent from Tables 2 and 3 that we were dealing with a changing situation, that our patient population was improving, and that even after 28 weeks we had no reason to feel that a plateau had been reached. How much further improvement our population would have shown had we continued to withhold drugs is certainly a matter for conjecture, and indeed for further experimentation.

Subgroup Formation for Drug Testing.—Phase I of our investigation was terminated at 28 weeks because of our intent to initiate testing of various combinations of drugs at that time. The information about our patients gained in Phase I was of immediate value in setting up our 16 experimental groups. For this we used Table 2, Column 6 ("Net Change"), classifying the patients into three groups on the basis of their net-change score. The first group included patients showing the greatest improvement;



Net change during Phase I as a function of initial rating. Changes designated by the minus sign (−) indicate improvement.

the second, patients showing an intermediate amount of improvement, and the third, patients who had shown little or no improvement or had actually got worse. Each of the 16 experimental drug groups, then, was set up to include one patient from each of these three "improvement" groups. It was further possible to establish the experimental groups so that their algebraically combined net-change scores were approximately equal. For example, three patients with respective net-change scores of −5, −2, and 0 were grouped together to form one of the 16 experimental drug groups, equal by algebraic summation, to each of the other 15 groups.

Comment

We have proposed that in any investigation into the effects of psychopharmacotherapeutic agents three sets of influences on the patient must be considered: the pharmacophysiologic, the psychologic, and the sociologic. It is patently impossible to assume that improvement in patients to whom drugs have been administered is due solely to the drugs themselves.

In all cases in which one wishes to learn the real value of a new drug, it is now considered appropriate to employ placebos with a patient-group that is more or less comparable to the group of patients receiving the active drug. As a further safeguard, it has become common to use the so-called "double-blind" technique, so that neither staff nor patients are aware to which patients the active agent has been given. These two developments, as far as they go, represent considerable advance on the level of the clinical trial in the evaluation of drugs to be used in psychiatry.

We do not wish at this time to enter into a discussion of the "double-blind" technique. It seems appropriate now, however, to consider certain aspects of the placebo which are borne on by the findings of our current investigation.

First, what constitutes an adequate placebo? It is a medication ordered by the doctor having the same apparent physical characteristics as the active agent, given by the same route of administration, yet not having the same specific therapeutic action. Ideally,

TABLE 3.—*Nursing Problems (Other Than Covered by Rating Scales) Posed by the Patient Population*

Type of Problem	No. of Patients		
	1st Week	12th Week	28th Week
Sleeping poorly	0	1	0
Eating poorly	17	12	9
Incontinent of urine	36	35	30
Incontinent of feces	25	21	15
Retentive of feces	1	1	0
Personally unclean	25	23	17
Total	104	93	71

the placebo should produce the same undesirable side-effects as the active agent, but this is rarely if ever achieved, if attempted. From the patient's point of view, he is given something by the doctor, via the nurse, or he has something done to him; he is treated the same as the other patients, to the extent that this is true in reality, or to the extent that he is able to perceive this. However, as the patients receiving the drug begin to undergo both physiologic and psychosomatic changes, he is undergoing only psychosomatic changes. Accordingly, his behavior and his symptoms are influenced differently, and it is on this basis that the experimenter may distinguish between the drug effect and the placebo effect.

Several investigators have shown that the placebo effect may be "quite powerful" and long-lasting.[3] Obviously, while the placebo effect may be extremely potent, the placebo itself can be nothing but impotent. Clearly, the placebo effect is due to psychosociologic factors attending placebo administration.

These psychosociologic influences are of two types. One group includes those specifically attending the administration of the placebo: the gift from or the attack by doctor or nurse; the implication that this drug will help the patient in some way; the modification of the patient's body image following administration of the placebo.

The second group of psychosociologic influences are those which exist prior to and concurrently with, but largely independent of, placebo administration. These include the effects of change of environment, new social group formation, doctor-patient interaction, and the general feeling of expectancy and enthusiasm in the experimental setting.

It is with the second group of psychosociologic influences that this paper has been concerned, since during Phase I of this investigation neither placebos nor active agents were administered. From the results of this phase it is apparent that these influences are potent, 39 of our 48 patients having shown improvement during this period. The fact that these influences exist, and the fact that they are potent, are not completely unfamiliar. Just how potent they are has now been quantitatively demonstrated, and we are now in a position to compare their effectiveness with that of an active agent.

In the later phases of this investigation, the same patient population is administered 16 combinations of drugs and placebos. How well or how poorly these various agents fare as compared with the "base line changes" herein described, which, as contrasted with "placebo effect," might be termed "milieu effect," will be reported in future communications.

Summary

In evaluating the usefulness of a drug in psychiatry, especially with a chronic hospital population, psychologic and sociologic influences must be identified and controlled in order to determine accurately how much of the patients' improvement can properly be attributed to the drug itself. In the present experiment a group of 48 chronic female catatonic schizophrenics, homogeneous in respect to age, color, duration of illness, physical condition, and prognosis, are studied on a special research unit for a period of 28 weeks prior to administration of drugs. During this period they receive general hospital care and are seen by us with sufficient frequency and intensity that evaluations of their behavior can be made on specially designed rating scales. It is found during these 28 weeks that 39 of the 48 patients show measurable improvement, 6 are unchanged, and 3 are worse. It is concluded that these changes are due to psychologic and sociologic factors, and that it is now possible to administer drugs and to distinguish between drug action per se and "milieu effect." It is argued that the use of placebos, while essential in drug research, does not permit a quantitative evaluation of psychologic and sociologic influences, and that only through establishment of a base line, as has been done in this investigation, can the actual value of drugs be properly determined.

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Perception: Equivalence, Avoidance, and Intrusion in Schizophrenia

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Observations and experiments on the nature of perception in schizophrenia have appeared at least since the time of Kraepelin [1] and Bleuler,[2] who variously and somewhat contradictorily claimed both change and no change in the perception of the schizophrenic. Others have pointed to specific sensory disturbances, for example, Rosenfeld [3,4] who felt stereognosis to be defective in catatonia. Few more recent writers, Arieti [5] excepted, have commented on the perceptual problem at all from the clinical standpoint.

Perception and Psychology

This relative dearth of papers recently fails to reflect the advances of the past few years in experimental perceptual psychology. Adams [6] as early as 1923 made clear that any simple stimulus-response formulation failed to make use of vital, but subtle, data in the relationship of the observed object to the memory of past experience, in that an object assumed to be a certain color from previous data persisted in appearing as the initial color despite marked change in the color of the object. She called this an "imaginal overlay." Cramer [7] reported similarly on projecting a blue color on a yellow screen such that it appeared gray, but if a child wearing a blue dress was projected on the yellow screen, it was seen distinctly as blue.

The suggestion that the equipment carried in one's head colored perception was noted by Bleuler [8] and was no doubt relatively well accepted in his own day, since his reference is merely *en passant* and no effort is made to defend or amplify it. Von Helmholz,[9] that arbiter of all things perceptual, made similar suggestions as long ago as 1866, but it remained for modern workers, such as Ames,[10] Cantril, Kilpatrick,[11] and others of the Princeton group to make considerably more explicit the attributes of the relation between the observed and the observer in perception. The presence of a preparatory mentalistic picture is primary in the notions of Hebb,[12] Vernon,[13] Woodworth,[14] and others.

From another area of experimentation, Klein [15,16] has pursued the subject of variations in percept based on apparent endopsychic differences, separating what he calls sharpeners from levelers on the basis of their availability to—or failure to—accept perceptual stimulus variations of small continuous nature. Klein has applied the word *Anschauung* to designate the anticipatory frame of reference with which the observer greets an object. Koffka [17] and the Gestalt school, generally, minimize the importance of the preceding experience of the perceiver. Among the neurophysiologists, Eccles,[18] Eddington,[19] and others have begun to depart from their usually rigorous treatment of the percept-concept continuum to suggest the importance of "mind influences" in the spatiotemporal response to events outside the individual.

The concept of "perceptual defense" is of interest in this regard also, as originally described by Postman,[20] who found that negatively valued stimuli had, under some conditions, higher thresholds than positively valued or neutral ones. In addition, it

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seemed that the prerecognition responses to the negative stimuli suggested a sort of avoidance. Postman [21] has more recently seen fit to subsume this observation under more general principles of perception, although Blum [22] suggests that the original formulation should not be so lightly cast aside.

Possible Perceptual Errors

From the standpoint of research in perception, then, there are several fundamental areas involved in any simple perceptual transaction, and perhaps many more in the complex transaction. These areas may be cited as (*a*) the presence or absence of the object, and (*b*) the attributes of the object in terms of the unfamiliar and the familiar elements in the observed object. Familiar elements provide immediate, and in the view of the Hanover group [11] purposive, alterations of a personal nature in the perceived object. The personal inner aspect of the perceptual process the Hanover people call "assumptive." They believe the assumptive set to be generally unconscious and actional in its effect on the object. It is the feeling of the Hanover (or Princeton) group that the assumptive set, derived as it is from past experience, implicitly inculcates a series of subjective probabilities, or expectancies, indicating relationships between perceptual events, and consequently significant in processes involving prediction in subsequent perceptual situations.

If these premises, simple as they seem, do comprise, in brief, the background for a percept, several sites for operative error are immediately apparent, putting aside failure of the stimulus. Errors of a receptive and interpretive nature might be listed as follows: (1) The perceptual apparatus may be absent or defective, altering perceptual input; (2) there may be some error in the transmission of the impulse so received to higher organizational elements; (3) once arrived at higher levels, the stimulus may or may not be accepted in terms consonant with the object or with the intent of the sender, depending upon the assumptive set of the recipient, or (4) accepting the message correctly, the recipient may reinterpret its inferences and direct them into secondary channels. From the standpoint of response, despite adequate cue acceptance and assimilation, there may be an improper expressive motor or verbal reply. Each of these areas may be subject to defect of some sort, but as yet the experiments to define precisely which or what combination of errors exists in any given instance have not been reported.

Perception in Schizophrenia

The purpose of this paper is to examine the areas of reception and interpretation of the perceptual input and to set forth a few generalizing principles which, from the standpoint of clinical psychiatry, seem apposite in rendering more meaningful some of our operations in therapy. Some aspects of the therapist's behavior and their subsequent effect on the patient will be examined.

If one accepts the idea that the schizophrenic is in a "world of his own," is "out of contact," several questions arise. First, how can the catatonic patient report so accurately the events occurring around him during his period of greatest abstraction if he is unaware? Second, it is quite obvious that patients, even in catatonic stupors, make responses to their environments, so that some interchange is evident. Such observations appeared as long ago as 1828.[23]

This responsiveness and recall on the part of the patient bring into question the concept of inaccessibility or accessibility in terms of the notion of ego boundaries. It is variously said that these are fluid, ill defined, or weak. Perhaps a better conceptualization would speak in terms of selective permeability, since often permeability seems the problem, with marked differences in what is permitted to pass through and what is not by some system of control, possibly at the disposition of the patient. And if by the term ego boundaries one intends, at least in part, that interface which opposes the outside world, one must include at this locus the apparatus

for dealing with impinging external percepts.

There are several possibilities for considing this surface contact with the outside world: Either the patient does not perceive what goes on around him (but we have evidence that he does, v. s.), or he perceives it and may handle the incoming percept in one of several ways. He may ignore it, ostensibly oblivious to even the most noxious stimuli,[24] or, if the patient does sentiently accept the stimulus, he must, as we all do, put it in some kind of alignment with concept systems already extant and available to him. If the patient is not psychotic, it is quite apparent his tolerance for information of an indifferent or novel character is generally greater. If he is psychotic, information (generally speaking, an agglomerate of external percepts) will be more rigorously required to fit into presently operative and more personally significant conceptual context. "Good morning," said to a relative normal, will rouse him from personal preoccupation to muster a similar remark in reply. "Good morning" to a psychotic may get no response, or quite a dramatic one, depending on the degree of abstraction, or such a one as, "It was a pretty morning on the day our Savior died"; or he may say simply "Good morning."

Certainly, there is then nothing weak, by which one might mean easily traversed, in the sensorial areas of the psychotic. He may, in apparent indifference to one's presence, masturbate; or, in indifference to his own body sensation, scratch at his skin until it bleeds, in automatic plucking. If deep thought and "great powers of concentration" are signs of mental strength in another, the psychotic's boundaries are clearly bolstered up with much secondary defensive shoring.

But it is common experience that on certain days or in certain situations the patient may be quite obviously more accessible; i. e., there may appear lacunae in the psychosis. There may be two possible explanations for this. One, the patient is more available to the novel or different thoughts of the therapist (but even on days of greater accessibility, it is generally that the increased freedom of accessibility is not so much that the patient is really more open to incursions from without as that he may be more willing to elaborate on his preoccupations and will be more accessible to relatively consonant, assuring comments from another). Generally, dissonant comments are still not acceptable.

Another possibility is that greater motor expression of a verbal nature is offered during the course of this perhaps (pseudo) communicative act. However, in both instances the autistic or personally oriented nature of the patient's behavior is quite apparent. This may even be indicated in the monologous way he may speak, allowing of no interruptions; or if he permits them, moving over the outsider's comment as though it had not been made, or taking off from it with further personal orientation, or getting up to walk away either in the middle of his own soliloquy or before an answer can be made at its end. The patient, of course, may pass long periods in silence, only abortively speaking or giving any sign of awareness. But it is our bias as therapists that if he is not answering, he is not listening, so readily must we be heeded; or if he answers differently from the way we expect, that he has no awareness of our intent or meaning, and is disoriented.

Accessibility in Schizophrenia

There is another possibility, as suggested above, that he must fit the external world into preexisting conceptual systems, and dare not or cannot respond in a frame of reference accessible to or consonant with a hostile outside world. This would be giving to the predatory world he sees about him the benefit of a direct answer in a context not the patient's, but someone else's, a thing palpably unsafe for the patient, isolated as he is in the diminishing archipelago of his thought world. It is curious, however, that this process of indifference, indirection, and distraction, initially a diffuse one involving

everyone, will eventually narrow itself down in the course of therapy so that one person either singles himself out, or is singled out by the patient, to be the bête noire of the patient's imago world, alternately his boon companion and his greatest enemy; and this will apparently, if he progresses, free the patient for more mutual contacts with less disquiet among the people around him.

This initial state of confusion quite common in acute psychosis may have a demonstrable physiological basis. From the work of French, Verzeano, and Magoun,[25,26] simultaneous stimuli from two different peripheral sources cause attenuation and occlusion in the reticular system. Mettler[27] believes that the locus of such a perceptual disturbance is the corpus striatum. If such data are analogous to psychological experience, it might help to explain the patient's sense of environmental competition and the resulting sense of chaos of which he may complain. It is also curious that often in the initial state of confusion, during which the patient may view everyone as part of a conspiratorial effort against him, his attitude may show a startling discrimination in what he will allow from the various levels of the people by whom he is surrounded. Tolerance of other members of the patient community is often remarkable. As one patient put it, staff are "monkeys" (men with keys) and patients are "donkeys" (fools without keys) and it makes a good deal of difference.

Thus the perception of the patient may be discriminating, depending on the level of intensity from which an approach is made (it may at times be easier to talk to another doctor, nurse, aide, or patient than to one's own doctor); perception may be halting or saltatory, that is, allowing only periodic and irregular entry of external intrusion; perception may be fragmentary, in which case part of the external world is allowed in only to the extent that it fits precisely with the standard preconceptions of the patient. It may be assumptive, in which case the *Anschauung* of Klein overflows its internal domains and makes assumptions regarding the behavior, ideations, or knowledge of the external world; this may take a projective form and the patient may attribute motives to the outside which may represent his own ideas, or they may be of an "empathically assumptive" nature, in which he imputes to the outside world special knowledge about himself which it may not actually have.

Referential Cueing and "Equivalence"

Usually one checks his ideas with the outside world, and if that world is normally responsive, a reply not precisely in conformity with it helps yield a contrast that sharpens perception and ideation. If we think of "chair" with our eyes closed, we will think of that chair in which we are sitting, a sort of composite idealized chair, or some chair or chairs we remember, becoming less precise in our image as the process progresses; in a sense, then, there is an "equivalence" of situations or objects as the opportunity for an external referential point becomes less explicit.

There are several situations where normally such imprecision leads to reduced use of outside referents and, consequently, greater symbolic equivalence of internal material. Thus, a man is a precise individual in reality, with singular identity, individual name, and characteristics, but in nonreferential phantasy he may be a bear, or one's father, husband, son, since the comparative or referential cueing of external perception is lacking. In schizophrenia, where the external referent is diminished in importance from within; in sleep, where perceptual modalities are muted, and in similar waking states, with artificial reproduction of the abeyance of external stimuli (Heron[28]; Lilly[29]); perhaps in the action of certain drugs, such as LSD, mescaline, bulbocapnine, and amines experimentally, and, interestingly enough, in the course of analysis at times, such external cueing seems absent.

In analysis, for example, the earliest impressions of the office may be quite vivid as one explores the perceptual boundaries of

the room; later the objective world of the office retreats into insignificance as one talks on, and the voice of the analyst initially accepted as a foreign body becomes assimilated to the extent that it almost appears to come from within, and not without, and the setting tends to support this illusion, which an audacious and mendicant stranger, such as a fly or a moth in the surroundings, or a symphony of automobiles from outside, may disrupt.

Avoidance of External Cueing

For certain obsessive people, the introspective act of looking in the mirror may be completely terrifying, so little will they allow any play of distracted phantasy. It is interesting that Bleuler,[2] in his description of the use of the so-called "foetal position," speaks of it as a position to ward off a maximum of external perceptual stimuli, with the greater part of the body surface concealed up under the patient. The psychotic uses many methods to avoid external matter. He will walk away, place hands over ears or mouth, close eyes, turn his back, shield his eyes, hide in a closet, or behind a pillow or object, put up a barrage of words, feign sleep, and, if nothing else works, attack with fists, chairs, words, feces, etc. At this point one can feel generally sure of having reached the patient; when he cannot put one off indirectly, actions may be substituted for words, and perhaps in the same affect-elucidating way. This last is a phenomenon which may be called pseudo-rejection, since it ostensibly aims at driving one off, but really tests the lengths one is willing to go to demonstrate love, interest, faith in the human hidden beneath the assaultive behavior. As one patient put it, "A hospital is a place where not nice people can go, where there are doctors and nurses who can tolerate their being not nice [violent]."

Intrusion in Therapy

There is an apparent tacit recognition of the problem of reorienting the distracted patient by making an intromission into his distantly departed soul * in all manner of folk tale, modern and primitive society. For example, to the primitive as to the psychotic, death equates to sleep, and the obvious method of treatment is loud noises, firecrackers, grotesque costumes, stroking him, dancing with him, incantations, etc. Similar techniques are used on the psychotic and the gods in the primitive mind. Even in this day, Zar dancers attempt to drive out demons possessing the body of the insane by attempting to glut almost every sensual modality; the Romans called the lares and penates and other gods in a loud voice. Even in our own stimulus-sodden society attempts are made to gain the initial wedge in the door, the contact that leads hopefully to meaningful communication and a return to health. One may touch the patient's skin, take his hand, talk to him of indifferent things, highly significant things, or merely generalizations about affect. One may jar him into awareness or out of a mood by some neutral or dissociate stimuli, like reading to him, beginning to sing an indifferent song, throwing a ball to him, etc. In one instance, maracas were used successfully to intrude upon a catatonic stupor.

Thus, the effect of music and dance therapies; the ameliorative behavior of a number of people and activities around, as in "total push"; perhaps even the radio or TV, shock therapy, and the newer drug therapies, such as use of reserpine (Serpasil) and chlorpromazine (Thorazine), which may act by reducing internal resistance and remove a block in transmission from the externally perceived world, fall into this category. Rhythmic sensory bombardment may represent an intrusive maneuver of a similar

* By way of contrast, during the course of an experiment on prolonged sleep deprivation, a number of the volunteer controls, when asked what they thought kept them awake so long, replied that they had a tendency to drift periodically into sleep, but that they could usually resist this tendency by concentrating on something, such as a game, throwing cold water on the face, getting into a conversation with someone, etc.

type.[30] This may be the underlying efficacy of greater disciplining, such as is found in state hospitals. It may suggest why the activist behavior of Rosen[31] is more intrusive and disruptive of psychotic operations than the more passivistic behavior of the analyst; it may have little or nothing to do with any theoretical constructs offered the patient except in a jarring sense. Rosen's work has been somewhat irreverently spoken of as "verbal shock treatment," and perhaps with good reason. Even periodically clearing one's throat; offering cigarets; moving objects; one's very physical breathing, staring, confronting presence, provide a perceptual intrusion. The patient may ask the therapist to look away. Very deteriorated patients apparently responsive to nothing else may jog back and forth to cadence with a loudly banged piano.

As well as proceeding as a first step in obtruding into the world of the patient, one must make him aware of his own responses, such as scratching or masturbating, in order that he may again begin to attend to stimuli of pain and other feelings from his own body, as a meaningful and significant source.

It is interesting how apparently indifferent stimuli may awaken quite a response. One patient, for example, refused regularly to speak when directly confronted with questions, but as soon as the therapist would begin working at something else or reading, a stream of conversation would flow from the patient. He may be vacantly gazing about the room, but let another patient come up to attract one's attention and the patient with whom one is sitting may throw something, begin a stream of abuse, etc. On the other hand, an excited patient may be enticed into a *Singfest* begun in the middle of a melee; he will stop to listen and join in; or doing something beside him, open to him, but not forcing, rather seducing, his attention will get him unthreatenedly engaged, though retarded in other contacts with him. One must direct all attention at other times toward the patient in order to convey to him his importance.

History of Intrusion

The notion of external intrusion was noted implictly by early psychiatric writers, such as Burrows[28] and Perfect,[32] in the 18th century, and the usefulness of reducing stimuli in the case of manics by seclusion, restraint, a darkened room, etc., was known to them also. The idea of external stimuli is certainly apparent in flogging, artificial infections and issues, refrigeration, dripping water, rotating chairs, swinging and gyration,[23] therapy which apparently goes back to Homeric times[32] (as in the case of Caelius, 72 A.D.). It was also known to Hippocrates[32] that the superimposition of infection will intercept the process of schizophrenia temporarily. A good example of this appears in the third case of Perfect.[32] Operations, and anesthesis, similarly free the psychotic, as does shock, for the acceptance of outside percepts in many cases for a longer or shorter time. Rush[33] describes a case of spontaneous cure, noting that the patient said with his first words: "I became aware of your interest in me several months ago but lacked the courage to speak up" (the significant word being "aware").

Acceptance of Referential Check Points

Patients ordinarily indifferent to outside percept may doubt their own senses when they first begin attending them, as in the case of a patient who asked me as a reference point whether it was as warm outside to me as she thought it was to her, when she first went outside after being in for some time. It is not only the doctor or nurses who may provide effectual external intrusion, but many other things ostensibly indifferent, such as an object in a room, an article in a magazine, the Bible, a line of poetry, a daily bath, a regular "good morning," the regular passage of some person under the patient's window, the death of a parent for whom the patient had much animus, a piece of clothing, a letter, the point where the doctor gives up, some amulet of significance around which the patient may orient himself.

A word might be said about the therapist in regard to the handling of perceptual material coming his way from the patient. Very often he is required to ignore his normal response to threat. He must, if possible, appear and try to be calm in the face of attack by the patient, since terror on his part would be perceived by the patient and might possibly frighten or panic him more. On the other hand, it might help in accomplishing the disruption of static-thought patterns desired by the therapist at times to admit fear. Perhaps this continual perceptual harassment in ignorance of his needs of personal safety is one of the elements which constitutes a definition of the idea "interest in the patient." This intrusive quality may also play a role in the common notion of "pointing out reality to the patient."

However, there is a point beyond which the pointing out of reality, confrontation attempts, and other perceptual essays pass the bound of neutral distraction, or attraction to us as indifferent, or noncharged objects or activities, and beyond which the consonant comment becomes highly dissonant and may even appear to the patient not merely intrusive but actually offensive, as an imminent attack to be warded off, and he in turn may react by attack. It does not matter whether the intrusion is really excessive or not, so long as he perceives it as such. It may be that tolerance for intrusion has a periodicity or rhythmicity, and interactive stimuli may, beyond a certain threshold, result in an explosion.

Since perceptual intrusion may be an early step in establishing contact, there remains the problem of the pertinency and permanency of such breach in the defense or the surface of the patient. The process of therapy after this is long and arduous, involving many vicissitudes. However, the regularity and reliability of this intrusion for the patient may begin to acquire the same significance that the initial appearance of the face of the mother begins to assume, and perhaps eventually achieves, in the eyes of the infant as it peeps over the crib wall. It is like a support, reference point, or framework on which other data may be hung and on the example of which other relations may be formed. It is like the Eiffel Tower of Paris or the Statue of Liberty. Around this symbol our world may be constructed, just as after being whirled around till we are dizzy, we try to focus on something which will help us to reorganize and slow down the rest of the world.

It is this focus or check point in the real world which may begin our orientation in terms of it and help us from the world of sleep or psychotic rootlessness. The referential intrusive object may return the psychotic to greater readiness to take a chance on other percepts that may help break through the rejection of external stimuli in preference for the half-world within, with its oceanic *Vorstellungen* and fluctuating meanings in unreferential equivalence.

Summary

An analysis is attempted of the place of perception in the world of the psychotic. Suggestions are offered describing the significance of certain apparently negligible acts in the course of daily contacts with schizophrenic patients, particularly those who may be withdrawn. Suggestions as to one of the effects of some of the hallucinogenic drugs are proposed, and a possible action of drugs, such as reserpine (Serpasil), is proposed.

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U. S. Army Psychiatric Training Program

Subsequent Nation-Wide Effects

GORDON R. FORRER, M.D., and JAMES L. GRISELL, M.A., Northville, Mich.

From their studies on the effects of the World War II Navy psychiatric training program, Caveny and Strecker [1] concluded that an intensive short course in neuropsychiatry had its effects on a group of physicians by making them, in general, more psychologically minded and appreciative of the psychiatric aspects of various illnesses with which they, as physicians, are confronted. The authors suggested that an intensive course in neuropsychiatry would provide an adequate number of psychiatrists to meet a wartime emergency and that such a course would be a source of needed psychiatrists throughout the country. They suggested that a similar training program could be instituted and conducted by other facilities, in need of psychiatric help, and that such programs would make physicians think of psychiatry as a career.

Present Investigation

The present study was embarked upon to evaluate the influence of the Army psychiatric training program on the subsequent professional careers of attending physicians. Questionnaires were sent to the 174 physicians who had attended the first four classes of the Army "8-0-10" neuropsychiatric training course. At the time of the survey, at least five years had elapsed since graduation from this Army-sponsored training course. No questionnaires were sent to men who graduated subsequent to 1950, since we were interested in the long-term influence of the program on the professional lives of the physicians and wanted to study this group after their professional career objectives had been stabilized.

In order to meet the critical shortage of psychiatrists, on duty with the Army, the Surgeon General's Office authorized the establishment of a neuropsychiatric training course. The facilities of the Medical Field Service School at Fort Sam Houston, San Antonio, Texas, and the clinical material from adjacent Brooke Army Hospital were selected. The length of the course was 16 weeks, during which time the didactic material usually contained in a two-year residency training program was presented both in psychiatry and in neurology. The psychiatric portion of the course was psychoanalytically oriented, and a great deal of care was exercised by the Surgeon General's Office in the selection of instructors.

Through the courtesy of the office of the Surgeon General and the Commandant of the Medical Field Service School, names and addresses of the graduates of the first four courses were made available to us. A letter, signed by one of us (G. R. F.), in his capacity as clinical director at the Northville State Hospital, accompanied each questionnaire. This letter specifically stated that the inquiry was not in any sense aimed at the procurement of medical personnel, in event of another emergency, but was solely for the purpose of securing data that might be helpful in formulating procedures should circumstances indicate the need for this. At the time of the survey, 30 states were represented, with the highest concentrations in New York, California, Texas, and Pennsylvania, in that order.

TABLE 1.—*Questionnaires Mailed and Returned*

Total physicians graduating from course	174
Total questionnaires mailed	174
Returned ("Unclaimed," "No forwarding address," etc.)	43
Total "live" questionnaires	131
Total questionnaires returned	91
Percentage of returns	69

Table 1 summarizes the situation in respect to questionnaires sent out and returned. The 69% of "live" questionnaires returned is exceptional, since it is the general consensus that a return rate of 50% is the usual result of a questionnaire survey. There can be no question, therefore, that there was a high degree of interest of those who had attended the "8-0-10" course in

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cooperating and making available the data for this study. Each question in the questionnaire was carefully studied and constructed so as to avoid bias and permit the maximum expression of opinion, insofar as this was consistent with the aim of the question in mind.

The first item on the questionnaire, "What is the nature of your medical practice at the present time?" was, following Caveny and Strecker's lead, deliberately presented without being constructed in specific categories, thus giving the physician latitude in describing the situation (Table 2). This Table reveals the general fields of practice reported in the 91 returned questionnaires. This factor appears to be especially significant, since the data to be presented later from other questions indicate that the course represented the starting point in neuropsychiatry for the majority of those currently engaged in that specialty. The finding that 59% of graduates remained in the field corresponds closely with Caveny and Strecker's studies in the Navy group, where 55% continued in this field of specialization.

TABLE 2.—*Nature of Current Practice*

	Number	Percentage
Psychiatry	54	59
General practice	16	17
Internal medicine	11	12
Other practices		
Neurology	3	12
Surgery	3	
Dermatology	1	
Pediatrics	3	
Anesthesia	1	

The questionnaire item "Did the Army neuropsychiatric program have any influence in determining the nature of your present practice?" brought forth the responses tabulated in Table 3. It is of some interest that only slightly over one-half of those now in psychiatric practice felt that the Army NP program had any influence in determining the nature of their present practice. The 20 physicians in the psychiatric group who said the course did not influence their present practice had their questionnaires studied in an effort to elucidate this high number. Seven of the twenty stated that they had decided upon psychiatry as a career prior to the Army psychiatric training course. All but 3 of the 20 had had previous experience in neuropsychiatry, so that undoubtedly the psychiatric training course served only to augment an interest which was already present. Among those psychiatrists who answered "doubtful," it was clearly apparent that all had decided the issue in regard to their future professional careers before taking the course. Table 4 presents the answers to the question "Have you found the NP training helpful in your present professional activity?" Of great interest in this table is the finding that both psychiatrists and nonpsychiatrists find that the training has been helpful, and in closely similar percentages (89% and 86% respectively). There were a large number of spontaneous comments praising the course and its con-

TABLE 3.—*Influence of Program in Determining Nature of Present Practice*

	No.	Yes		No		Doubtful	
		No.	%	No.	%	No.	%
Psychiatric group	54	29	54	20	37	5	9
Others	37	10	27	23	62	4	11

TABLE 4.—*Answers to Question: "Have You Found the NP Training Helpful in Your Present Professional Activity?"*

Type of Practice	No.	Yes		No		Doubtful	
		No.	%	No.	%	No.	%
Psychiatry	54	48	89	1	2	5	9
Others	37	32	86	2	5	3	8

TABLE 5.—*Answers to Question: "Prior to Your Taking the NP Course, Had You Had Experience in Neuropsychiatry?"* •

	Yes		No	
No.	No.	%	No.	%
54	18	33	36	67

• Psychiatric group only; does not include medical school and internship.

tribution to the graduates' professional life and, remarkably, no derogatory statements. The internists were especially emphatic in the beneficial influence of the course on their professional lives.

Table 5 tabulates the answers from the group specializing in psychiatry to the question "Prior to taking the NP course, had you had experience in neuropsychiatry?" When psychiatric experience during medical school and internship was excluded, only 33% of the group who eventually went into psychiatry had had prior experience in this specialty. These findings lead us to conclude that the Army program represented the first intensive organized contact with neuropsychiatry for the majority of the group who continued in psychiatric practice.

TABLE 6.—*Psychiatric Training Subsequent to That of NP Program* •

		Yes		No	
Type of Practice	No.	No.	%	No.	%
Psychiatry	54	52	96	2	4

• Percentage of psychiatric group had three years or more of subsequent training.

Since our interests were concerned mainly with those who had continued in psychiatry subsequent to graduating from the Army psychiatric training course, this group was studied in terms of how much training had been acquired subsequent to graduation. Table 6 tabulates those who are currently in the practice of psychiatry who had three or more years of subsequent training. All but two men completed three or more years of subsequent training. The high degree of motivation and interest in the field of psychiatry is evident when one considers that two-thirds of the NP group had had no substantial psychiatric training prior to the Army training course. Table 7 tabulates those answers to the question "Are you Board-certified?" Board certification of 61% of those who completed the Army training course is an extremely gratifying figure, about twice that found by Caveny and Strecker in their study of Navy graduates. Both studies were conducted with the same time interval, of five years, between the last graduating class and the questionnaire survey. Whereas all other figures compare reasonably closely with the findings of these authors, this discrepancy in the number of Board-certified men in psychiatry is surprising and puzzling. We can offer no satisfactory explanation for this. Perhaps there are significant differences in the two groups that are not apparent. Table 8 presents the situation in regard to psychoanalysis for the group continuing in psychiatry. It seems highly significant that 78% of all men continuing in neuropsychiatry have completed, are currently in analysis, or plan analysis in the future. This factor was not studied by Caveny and Strecker, and no comparison is possible between the Navy graduates and the Army graduates. In marked contrast to this, in the nonpsychiatric group, only two have

TABLE 7.—*Board Certification*

		Yes		No	
	No.	No.	%	No.	%
Psychiatry	54	33	61	21	39
General practice	15	1	7	14	93
Internal medicine	11	2	18	9	82
Neurology	3	2	67	1	33
Other specialties	8	3	37	5	63
Neurology + other specialties	11	5	45	6	55

TABLE 8.—*Psychoanalysis (Psychiatric Group Only)*

	No.	Percentage	
Plan analysis in future	8	15	78%
Currently in analysis	18	33	
Analysis completed	16	30	
None contemplated	12	22	
Total	54		

completed analyses and two are currently in analysis. The extent and degree to which the course influenced the psychiatric group in regard to psychoanalysis were not determined by the questionnaire.

In view of the fact that Caveny and Strecker estimated that "a better than fair estimate would place considerably more than half of the total enrolees on the selected basis," we sought to get at the question by asking "How did you get assigned to take the NP course?" Table 9 tabulates the 91 returned responses in regard to this item. It will be seen that the Army group differs considerably from the Navy group by virtue of the fact that some 86% of them volunteered for the course. This seems of significance, since closely similar percentages of men continued in psychiatry after completing the course, and this irrespective of the fact that a far higher percentage of the Navy attendees were ordered to attend. One would have anticipated that, because of the enforced nature of attendance in a high percentage of those attending the Navy course, there would have been fewer men continuing in psychiatry subsequent to graduation. This, however, is not the case and suggests that volunteer selection has little, if any, influence on the subsequent career choice of physicians trained in psychiatry in a military setting.

TABLE 9.—*Answers to Question: "How Did You Get Assigned to Take the NP Course?"*

	No.	Percentage
Volunteered	78	86
Ordered to attend	13	14
Total	91	

Aware of the fact that, regardless of how good a training program might be, it is useless unless the graduate is placed in a position which utilizes that training, we asked the question: "Following completion of the NP course were you assigned to NP duties?" It is extremely gratifying to see, in Table 10, that 91% of those men answering the questionnaire were assigned to psychiatric duties following completion of the course. Careful review of those eight questionnaires which indicated that the NP graduate was not assigned to psychiatry was rather revealing. One man spent half of his remaining service time in psychiatry and the other half in an administrative position. Two men were placed on orthopedic services. Four were assigned to posts for which their training prior to the NP course fitted them. One was assigned to nonpsychiatric duty with no obvious reason apparent.

TABLE 10.—*Answers to Question: "Following Completion of the NP Course, Were You Assigned to NP Duties?"*

Answer	No.	Percentage
Yes	83	91
No	8	9
Total	91	

Summary

Questionnaires were sent to physicians who were enrolled in the Army's four-month intensive training course in neuropsychiatry during the period 1946-1950. Of the 131 "live" questionnaires, 91 (69%) were returned. 1. Returns indicate that 59% of the group have continued, to date, in the practice of psychiatry. 2. More than half (54%) of the psychiatric group were favorably influenced by the program in determining the nature of their present practice. 3. Eighty-nine percent of the psychiatric group and 86% of the nonpsychiatric group found the NP training helpful in their present professional activity. 4. Only 33% of the psychiatric group had had any substantial exposure to psychiatry prior to the NP course. 5. Ninety-six percent of those continuing in psychiatry had completed three years or more of subsequent resident training after graduating from the Army psychiatric training course. 6. Sixty-one percent of all men continuing in psychiatry are currently Board-certified. 7. Seventy-eight percent of the psychiatric group have completed analysis, are currently in psychoanalysis, or plan analysis in the future. 8. Ninety-one percent of those

returning questionnaires indicated that the physician had volunteered to take this psychiatric course.

Conclusion

From the above data, we draw the inference that an intensive training course in psychiatry has a definite beneficial influence on the professional lives of physicians. There appears to be no substantial difference in the influence of the training course on the subsequent careers of physicians whether they are ordered to attend the course or whether they take the course voluntarily. Those who graduate from such a course appear to be stimulated to continue further training in an outstandingly high percentage of cases.

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Notice

Material supplementary to the article entitled "Intracerebral Procaine as Prognostic Test for Prefrontal Lobotomy," by Dr. Isidor W. Scherer and Dr. John F. Winne, in the August issue of the ARCHIVES, page 220, has been deposited as Document number 4988 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35 mm. microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

Diagnostic Testing for Cortical Brain Impairment

EPHRAIM S. GARRETT, M.D.; A. COOPER PRICE, Ph.D., and HERDIS L. DEABLER, Ph.D., Biloxi, Miss.

In 1955, the Spiral Aftereffect Test was presented as a means of diagnosing organic brain involvement.[3] This procedure was earlier used by Freeman and Josey as an indicator of memory impairment.[1] The test consists of rotating an Archimedes spiral figure for 30 seconds, after which the rotation is stopped. Normal subjects perceive a vivid negative after-image of apparent motion, the spiral line being seen as either expanding or contracting, depending on the direction of rotation of the spiral figure prior to being stopped. It was found that subjects with known organic brain damage, particularly those with cortical involvement, were unable to perceive or had difficulty in perceiving the distinctive after-effect.

The results of the experimental research for the diagnosis of cortical brain damage by means of the spiral after-effect were highly significant. However, 2% of the patients with organic impairment did obtain scores within the normal test limits, and in follow-up studies this same approximate percentage has been observed. Although approximately 98% of the cases studied have been diagnosed validly, the possibility of using another test of high validity to form an appropriate diagnostic battery is proposed. The rationale of overlapping tests which would increase the reliability and validity coefficients and contribute uniquely by adding a quantitative range is thought to be valid.

For some time the neuropsychiatric patients in the hospital and domiciliary sections of this center have had the Graham and Barbara Kendall Memory-for-Designs Test[2] administered during examinations. In general, the test appeared to be very useful in diagnostic work with patients of suspected cortical brain impairment. It provided a quantitative dimension of from 1 to 40-plus points, which was useful in revealing the degree of impairment. Furthermore, it required but a few minutes to administer.

In addition, it provided a learning situation, a measure of psychomotor coordination, and a positive perceptual after-effect. These elements, while overlapping to a certain extent with the perceptual phenomenon of the spiral after-effect, were also considered to contribute additional diagnostic data.

Therefore, the Memory-for-Designs Test was selected for use with the spiral after-effect to increase validity and reliability of diagnosis of cortical brain damage when this battery was administered.

In a brief pilot study using the Memory-for-Design Test, a few of the cases with chronic brain damage earned scores of 9 and 10 points, which was only borderline, according to the interpretation in the test manual. The possibility that the previously stated range of 5-11 for borderline diagnosis might be too broad was considered as another reason for the research investigation.

Method

Apparatus.—An electric motor and stand commonly used for color-mixing experiments was used to produce the necessary rotation. To the shaft, an opaque disk of white plastic 6 in. in diameter was attached. An Archimedes spiral of 920 degrees, or two and one-half circuits about the center, was constructed of dark-colored plastic and was placed against the white disk background. The spiral was reversed for the effect of opposite rotation. The disk was turned at approximately 100 revolutions per minute. It was later found that a spiral could

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be rotated on a phonograph turntable of 78 rpm with identical results.

Procedure.—Testing took about five minutes per S and was conducted only in the daytime, when illumination was good. The S was seated approximately 8 ft. from the apparatus. Standard instructions were given immediately preceding the test as follows: "This is a special eye test (so stated in order to get attention and cooperation from psychotic Ss). Look at the center (pointing) and don't take your eye away until I tell you to." Then the rotation was begun. Spiral B, giving normal Ss a negative after-effect of contraction, was presented first for 30 seconds. This seems to be the more difficult of the phenomena, and, by presenting it first, the possibility of guessing what the next after-effect should be is decreased. Thirty seconds was ample time for normal and other Ss. While the disk was rotating, S was asked "What does the line appear to be doing?" This was done to make sure S was attending and could report his experience. After 30 seconds, the disk was stopped and S was then asked immediately, "Now what does the line appear to be doing?" The patient's answer was recorded. The routine was repeated with the spiral reversed (Spiral A), giving normal subjects a negative after-effect of expansion. This was followed by a repetition of presentation of Spiral B, then A, for a total of four trials of 30 seconds each. Each normal report, that is, seeing the negative after-effect correctly, was scored 1. Each abnormal report, that is, failure to perceive the negative after-effect, was scored 0. Reports of after-effect in which no apparent change of dimension occurred but in which apparent motion forward or backward was reported were given a score of ½. The Ss scored a total of 4, 3, 2, 1, or 0, depending on the degree of their perception of the after-effect. In the case of normals the negative after-effect was so immediate and vivid that it was scarcely necessary to conduct the usual inquiry for scoring. There was little ambiguity as to the presence or absence of the after-effect with most Ss.

Strict adherence to the procedure for the testing of Ss was exercised. It was believed that variations from the standard directions might have considerable bearing upon the validity of the results obtained. Precaution was taken not to suggest or structure in any way the nature of the perception being investigated.

The Memory-for-Designs Test was given according to the directions contained in the Manual.[2]

Forty cases of known cortical brain involvement were used in the experimental organic group. Diagnosis of these cases had been established by hospital staff action. The group included cases of chronic brain syndromes associated with post cerebral accident, trauma, drugs, chronic alcoholism, cerebral thrombosis, cerebral hemorrhage, cerebral arteriosclerosis, and CNS syphilis. The age range was from 44 to 84 years.

The normal sample was composed of 30 subjects (20 men, 10 women), ranging in age from 20 to 54. They were from the medical, nursing, and administrative staff of the hospital.

Results

Scores of subjects on the Graham Kendall Memory Test are given in Table 1.

TABLE 1.—*Graham Kendall Scores*

Errors	Chronic Brain-Syndrome Subjects	Normals
0	0	23
1	1	3
2	1	2
3	1	1
4	2	1
5	0	0
6	0	0
7	0	0
8	2	0
9	0	0
10	2	0
11	2	0
12	2	0
13	1	0
14	1	0
15	2	0
16-20	3	0
21-25	6	0
26-30	4	0
31-35	3	0
36-40+	7	0
Total no. of subjects	40	30

The five subjects who had normal scores on the Graham Kendall Test had pathological scores on the Spiral Aftereffect Test. They were clinically diagnosed as organic cases.

TABLE 2.—*Spiral Test Scores*

Score	Chronic Brain-Syndrome Subjects	Normals
0-½	7	0
1-1½	6	0
2-2½	15	0
3-3½	11	0
4	1	30
Total no. of subjects	40	30

All of the normals earned a score of 4 on the Spiral Test. Only 2.5% of the organic group were able to obtain a score of 4 on the Spiral Test. In the event that one test of the battery failed to agree wtih the established diagnosis, the other test revealed the impairment, so that practically all

of the cases studied were accurately evaluated by the battery.

Comment

Some of the relative advantages and disadvantages of both tests were revealed in this study. The Spiral Aftereffect Test lacks a broad quantitative dimension for the evaluation of the degree of organicity, even though its validity is extremely high.

On the other hand, the Memory-for-Design Test cannot be given to subjects who are severely crippled. Patients who have difficulty in using their hands and arms are penalized by the test in that they lose the perception of the figure while they are trying to draw the figures, partly owing to the greater elapsed time. Also, tremulousness of the hands may produce drawings which are so poor that they present a false impression of the actual degree of intellectual impairment.

Generally, the Spiral Test falls into the category of phenomenological movement, which is a primary sensory phenomenon. It does not consist of the displacement of a sensation as an object is moved through space. It is immediately given, and all perceived movement can be interpreted as ϕ-phenomena. When there is no actual physical movement, the experience, as in the case of the Spiral Aftereffect Test, is a nonveridical or illusory one.

The preceptual processes involved by the Memory-for-Designs Test may be explained by gestalt concepts. According to this theorem forms not only establish themselves as a process of the brain but tend to persist through time. A "trace" is said to exist as a residue of the stimulus-excitation process. Isomorphism is invoked to explain the corollary between the stimulus-excitation and the trace-concept. The immediate stimulus process engenders a field excitation directed toward a trace of an earlier process, and it is the trace which is the physiological basis of conscious memories. Traces themselves are not in consciousness.

Summary and Conclusion

By using both the Spiral Aftereffect Test and the Graham Kendall Test, the diagnosis of cortical brain impairment is greatly facilitated. Cases missed by one are detected by the other test. The two supplement each other and together make a highly valid battery for determination of cortical involvement.

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Books

BOOK REVIEWS

Psychology, Psychiatry, and the Public Interest. Maurice H. Krout, Ph.D., Editor. Price, $4.00. Pp. 217. University of Minnesota Press, 10 Nicholson Hall, Minneapolis 14, 1956.

The recent controversy concerning who should do psychotherapy has continued and intensified. Attempts at compromise and cooperation seem to have been unsuccessful in settling the issues. In some states legal action is either in process or contemplated. The interprofessional quarreling, of course, has affected the public interest, and it is to this point that Krout has oriented a small volume to which a number of authorities in the field of psychotherapy have contributed. Krout himself is a psychologist, and it is, therefore, not surprising that of the fifteen contributors all are psychologists except one. It is inevitable that the articles should be slanted toward the psychologist's point of view, but, nevertheless, the editor and the contributing authors have dealt with the problem in an objective and reasonably fair manner. The book is recommended to all those concerned at the present time with the problem of lay therapy and especially psychotherapy by clinical psychologists.

Group Processes. Transactions of the Second Conference, Oct. 9-12, 1955, edited by Bertram Schaffner, M.D. Price $3.50. Pp. 255. Josiah Macy, Jr. Foundation, 16 W. 46th St., New York, 1956.

In this, as in most of the Macy Conference reports, there is a wealth of fascinating multidisciplinary discussion, extremely valuable for students of the topic under discussion. In this volume, Sladen describes social structure among penguins, Blauvelt discusses neonate-mother relationship in goat and man, and Bateson talks about the message "This is play." Apparently, a film demonstration for the kinesic analysis of behavior of children presented by Birdwhistell was not subject to much comment.

Each one of these authors presented fascinating expositions, if only the conference members had permitted them to get on with their presentations, or at least if the editor had deleted the premature questions and disturbing remarks of the audience. The conference may be a good tool for communications among the participants, and each learns a great deal—but when, oh when, will Dr. Frank Fremont-Smith learn that this format is no good for the readers of the published proceedings?

Dynamic Psychiatry in Simple Terms. By Robert R. Mezer, M.D. Price, $2.50. Pp. 174. Springer Publishing Company, Inc., 44 E. 23d St., New York 10, 1956.

This is truly a book in simple terms, sometimes so simple in content and form that one wonders about the intellectual level of the modern medical students to whom it is addressed. It is also simple in extent, since the subject matter is quite restricted and the field is severely amputated. The reviewer doubts that this book is an answer to the faculty's bemoaning for a satisfactory textbook. Psychodynamics is a complicated and difficult subject. Dedicated teachers are necessary for the sparkle of enthusiastic interest to be conveyed to students, using examples from personal experience and of topical interest. It is a subject that cannot be talked or written down to an immature level, such as the passage on page 147: "Life begins with birth. Once born, the baby must begin to live life."

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1. Vischer, T.J.: *Unpublished data from* Clinical Study of Proclorperazine, a New Tranquilizer for the Treatment of Non-Hospitalized Psychoneurotic Patients.

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*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.